Title: A contemporary picture of enterococcal endocarditis: prospective study of 516 cases from the GAMES Cohort

Short Title: Prognostic factors of enterococcal endocarditis

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Abstract

Background: Enterococcal endocarditis (EE) is a growing entity in Western countries. However, quality data from large studies is lacking.
Objectives: To describe the characteristics and analyze the prognostic factors of EE in the GAMES cohort.
Methods: Post-hoc analysis of a prospectively collected cohort of patients from 35 Spanish centers from 2008 to 2016. Characteristics and outcomes of 516 cases of EE were compared to those of 3,308 cases of non-enterococcal endocarditis (NEE). Logistic regression and Cox proportional hazards regression analysis were performed to investigate risk factors for in-hospital and one-year mortality, and relapses.
Results: Patients with EE were significantly older, presented more frequently chronic lung disease, chronic heart failure, prior endocarditis, degenerative valve disease and had higher median age-adjusted Charlson score. EE more frequently involved the aortic valve and prosthesis (64.3% vs. 46.7%; P<0.001; and 35.9% vs. 28.9%; P=0.002, respectively) but less frequently pacemakers/defibrillators (1.5% vs. 10.5%; P<0.001), and showed higher rates of acute heart failure (45% vs. 38.3%;P=0.005). Cardiac surgery was less frequently performed in EE (40.7% vs.45.9%;P=0.024). No differences in in-hospital mortality and one-year mortality were found, whereas relapses were significantly higher in EE (3.5% vs. 1.7%; P=0.035). Increasing Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications were risk factors for mortality, whereas prior endocarditis was protective and persistent bacteremia constituted the sole risk factor for relapse.
Conclusions: Besides other baseline and clinical differences, EE more frequently affects prosthetic valves and less frequently pacemakers/defibrillators. EE presents higher rates of relapse than NEE.

Condensed abstract: Enterococcal endocarditis (EE) is a growing issue in Western countries. By comparing 516 cases of EE with 3,308 cases of NEE, we found older median age and higher comorbidity rates among EE than in NEE, as well as higher rates of aortic valve and prosthetic valve involvement, and heart failure. Mortality did not significantly differ between EE and NEE, whereas relapses were higher in EE. Risk factors for mortality in EE were Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications, whereas persistent bacteremia was associated with a higher likelihood of relapses.

Keywords: Infective endocarditis, enterococci, heart failure, relapses, prosthetic valves, epidemiology.

Abbreviations: CNS, central nervous system; EE, enterococcal endocarditis; HCA, healthcare-associated; IE, infective endocarditis; MRSA, methicillin-resistant *S. aureus*; NEE, non-enterococcal endocarditis; PCM/DF, pacemakers/defibrillators; TAVI, transaortic valve implantation; TEE, transesophageal echocardiography

Introduction

Enterococci have been identified as a growing pathogen, primarily in health-care associated infections in the U.S., where vancomycin-resistant strains pose a serious challenge to the health system [1]. However, enterococci are also playing an increasingly important role in infective endocarditis (IE) [2], with most recent series placing it as the third leading causative agent in high-income countries, reaching up to 15-20% of total cases [3-6]. Moreover, enterococci are the leading causative agent of transaortic valve implants (TAVI)-associated IE [7].

Most cases (around 90%) of enterococcal IE are caused by *E. faecalis* [8]. Since the turn of the 21st century, the classically described clinical presentation of enterococcal IE as a community-acquired, subacute pauci-symptomatic disease of genitourinary source [10] is progressively turning in a more aggressive, acute, more frequently healthcare-associated (HCA) disease of occurring predominantly amongst elderly patients with a large burden of comorbidities and seldom a clear identifiable source. [9,10].

The focus of recent relevant studies addressing enterococcal IE is largely placed on the genetic and molecular aspects [11,12], impact of antimicrobial resistance (e.g. vancomycin, high-level aminoglycoside resistance and daptomycin resistance) [1,8,11,12], therapeutic options [13-15] or the use of TEE to detect IE [16-18], whereas there is a relative paucity of studies explaining the main clinical and epidemiological changes of enterococcal IE in the last two decades and their underlying mechanisms, such as its potential association with colorectal neoplasms [19,20].

We aimed to investigate the main characteristics of enterococcal IE in a cohort of 516 patients prospectively collected from 2008 to 2016 and to compare them with those of non-enterococcal IE.

Methods

Design: multicenter prospective observational study including 35 Spanish centers between 2008 and 2016. The characteristics of the GAMES cohort, collection of data variables through a specific central registration depository, and definitions are described elsewhere [5]. The work-up for searching potential sources of the infection, including gastrointestinal tract screening, was not systematic but was decided by the treating physician. Persistent bacteremia was defined as positive blood cultures beyond seven days of effective antibiotic therapy; relapse refers to a new episode of IE due to the same microorganism within the next 6 months after the initial episode; acute renal failure was defined in the data collection sheet as a worsening equal or higher than 25% of serum creatinine or glomerular clearance occurring within a lapse of 72h; community-acquired IE was defined as IE diagnosed within the first 48 hours of admission in a patient who did not fulfill the criteria for HCA infection. HCA infection encompasses nosocomial and non-nosocomial HCA IE [21]. Nosocomial IE was defined as IE in a patient who had been hospitalized for >48 hours before the onset of signs or symptoms consistent with IE. Non-nosocomial HCA IE was an IE diagnosed within 48 hours of admission of an outpatient.

Patients: adult individuals with definite or possible IE diagnosed according to the modified Duke criteria [22].

Outcomes: in-hospital and one-year mortality (death due to any causes within 30 days and 365 days from the admission, respectively), and relapses.

Statistical analysis: Categorical variables were summarized as percentages and continuous variables as means and standard deviations. Categorical variables were compared using the chi-square test (or Fisher's exact test where necessary). Continuous variables were compared using the Kruskal-Wallis test. Cox proportional hazards regression analysis was utilized to investigate risk factors for one-year mortality and relapses. Variables with $P<0.20$ in the

univariate analysis were included in the models. Kaplan-Meier survival curves free of mortality at one year and relapses were generated with log-rank test analysis and considering censored episodes according to the time measured for each endpoint. A two-sided $P<0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Patients with enterococcal IE were significantly older and had higher rates of comorbidities, leading to a significantly higher median age-adjusted Charlson score (**Table 1**). Diabetes mellitus, chronic lung disease, congestive heart failure, previous IE, and non-congenital valve disease were all significantly more frequent among enterococcal IE, whereas ischemic cardiomyopathy and chronic renal failure, although more frequent too among enterococcal IE, did not reach statistical significance. On the other hand, iv drug use, HIV infection and congenital heart abnormalities were significantly more common among patients with non-enterococcal IE. The proportion of prosthetic valve IE was significantly higher in the enterococcal IE group, whereas PCM/DF-associated IE was significantly more frequent in the non-enterococcal IE group. The aortic valve was significantly more frequently involved in enterococcal IE cases, while the tricuspid and pulmonary valve were more commonly affected in non-enterococcal IE. Around half of the cases in both groups had an unknown source of the infection. The median time elapsed between the appearance of symptoms and hospital admission was not different between the two groups. Genitourinary and gastrointestinal foci were significantly more common among enterococcal IE episodes; meanwhile, oral, vascular and cutaneous sources were significantly more frequent in the non-enterococcal IE group. *E. faecalis* caused 90.7% of cases in the enterococcal IE group, being *S. aureus*, coagulase-negative staphylococci, and viridans group streptococci the more frequent causative agents in the non-enterococcal IE group. As for the proportion of cases from the global cohort, *S. aureus* represented 22.8%, coagulase-negative staphylococci 17.4%, viridans group streptococci 16.1%, enterococci 13.5%, Bovis group streptococci 6.4% and other streptococci 5%. Enterococci accounted for 9.5% of cases in patients aged less than 65 years and 16.4% among patients ≥65 years old (P<0.001). There were no cases of enterococcal IE caused by vancomycin-resistant enterococci. The site of acquisition did not

significantly differ between the two groups. Clinically, non-enterococcal IE presented with significantly higher rates of extensive CNS emboli, pulmonary emboli, and septic shock, as well as perivalvular abscesses, intracardiac fistula and pseudoaneurysm in the echocardiography, whereas enterococcal IE presented significantly higher rates of new onset heart failure and splenic abscesses. Enterococcal IE received a significantly longer median time of antibiotic therapy (42 vs. 36 days; P<0.001), being rates of cardiac surgery higher among non-enterococcal IE patients. Remarkably, 8 patients in the enterococcal IE group did not undergo cardiac surgery when indicated due to advanced liver disease, whereas this happened in 21 patients in the non-enterococcal group (1.5% vs. 0.6%; P=0.025, not shown). In-hospital and one-year mortality did not differ between both groups, yet relapses were significantly higher among patients with enterococcal IE.

The characteristics and outcomes of enterococcal and non-enterococcal IE are compared in the Supplementary material among native valve IE cases (**Supplementary Table 1**), prosthetic valve IE cases (**Supplementary Table 2**) and patients undergoing cardiac surgery (**Supplementary Table 3**). Notably, both in-hospital and one-year mortality were significantly higher among patients with non-enterococcal prosthetic valve IE, whereas relapses were significantly higher among patients with enterococcal prosthetic valve IE.

A comparison of HCA vs. community-acquired enterococcal IE cases is shown in **Table 2**. Notably, HCA enterococcal cases more frequently involved prosthetic valves and had higher rates of chronic liver and renal disease, including dialysis, and transplantation, and immunosuppres therapy, whereas community-acquired enterococcal IE involved native valves significantly more frequently and presented higher rates of iv drug use and HIV infection. Outcomes did not significantly differ between the two groups.

The characteristics and outcomes of enterococcal IE caused by *E. faecalis* are compared to those enterococcal IE cases caused by other species in **Table 3**. Of note, patients with *E.*

198 *faecalis* IE showed a trend to elder ages and presented significantly higher rates of chronic
199 congestive heart failure, chronic dialysis, prosthetic valve IE, and paravalvular abscess.
200 Patients with *E. faecalis* IE significantly received as initial antibiotic treatment double beta-
201 lactam combinations, whereas there were no differences between groups associated with
202 beta-lactam plus aminoglycoside initial combinations. Non-*E. faecalis* IE was more
203 frequently treated with other type of antibiotic treatment, being vancomycin combined with
204 an aminoglycoside the third most common combination among *E. faecalis* IE patients. Ten
205 (62.5%) of the 16 relapses occurring in patients with *E. faecalis* IE had received double beta-
206 lactam therapy, 5 (31.2%) received beta-lactam plus aminoglycosides and 1 (6.3%)
207 vancomycin plus gentamicin. The two relapses occurring in non-*E.faecalis* IE patients had
208 received other type of combinations. Outcomes did not significantly differ between the two
209 groups.
210 In the multivariate analysis, increasing age-adjusted Charlson score, paravalvular
211 complications, new onset of heart failure, septic shock and logistic EuroSCORE were
212 identified as risk factors for one-year mortality and prior episode of IE was protective.
213 Persistent bacteremia was identified as a risk factor for relapse (**Table 4**). Curves for mortality
214 and relapse over time are shown in the **Central Illustration**.
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Discussion

Epidemiology and main clinical characteristics

Ours is the largest national series of enterococcal IE described to date. In terms of epidemiological findings, this study confirms some of the common traits of the enterococcal IE profile described in studies conducted during the last fifteen years, but we also found some differences in this regard. Remarkably, as foreseen in the previous literature, median age, female sex, comorbidities, unknown source of infection and healthcare acquisition among enterococcal IE cases are on the rise. For example, Chirouze et al provided data on 500 cases of enterococcal IE from the International Collaboration on Endocarditis (ICE) collected from 2000 to 2006 and compared them with 823 cases of IE caused by oral streptococci and 293 cases of D group streptococcal IE [4]. North America was the region where more cases of enterococcal IE came from (50%), 90.6% of cases were caused by *E. faecalis*, median age was 65 years, 72.6% of cases occurred in men, 22.4% had diabetes, 8.4% were on chronic hemodialysis, 11.2% had cancer, 12.5% of cases had a prior episode of IE, 23.4% of cases overall were healthcare-associated and enterococcal IE involved prosthetic valves (in 29.1% of cases) significantly more frequently than streptococcal IE [4]. As in the case of another study from the ICE [23], we found that enterococcal IE is significantly more frequent among patients aged 65 years or more. By comparing to all other etiologies of IE, we have also identified that enterococcal IE is significantly less frequent among iv drug users, people living with HIV, patients with congenital heart disease, whereas it significantly more often the aortic valve and affected people with chronic diseases such as respiratory diseases, ischemic myocardiopathy, chronic heart failure, chronic renal disease or degenerative valve disease.

From a clinical standpoint, the two major findings of our study are the high rate of prosthetic valve involvement and heart failure. In addition, we found that in spite of presenting very

similar profiles in all other aspects, *E. faecalis* produced significantly more prosthetic valve IE cases than other enterococcal species while the latter produced significantly more native valve IE, which has not been noted before.

Complications and outcome

Heart failure was a prognostic factor for mortality among patients with EE. However, when analyzing native and prosthetic valve IE separately, we did not find higher heart failure rates in prosthetic enterococcal IE. Heart failure as a common trait of enterococcal IE has previously been defined in some reports [24,25] but remarkably not in the Chirouze et al study [4]. In our cohort of enterococcal IE, we also find higher rates of moderate-severe aortic and mitral regurgitation than in other types of IE. We hypothesize this might be due to the higher frequency of heart abnormalities of elderly patients rather than to a special ability for valve tissue destruction inherent to enterococci, which is consistent with the lower rates of paravalvular complications we observed among patients with enterococcal IE and the fact than the median time elapsed from the onset of symptoms to admission was not different between enterococcal and non-enterococcal IE.

Whereas we did not find significant differences in in-hospital and one-year mortality between enterococcal and non-enterococcal IE overall, both were significantly lower in enterococcal prosthetic valve IE than in non-enterococcal prosthetic valve IE in spite of the aforementioned lower rates of cardiac surgery.

Although enterococcal IE classically presents with higher rates of relapse than other types of IE [8], the risk factors associated with this phenomenon have been scarcely investigated to date. Moreover, no other large study on enterococcal IE had previously confirmed a significantly higher rate, including the ICE study led by Chirouze, which did not provide data on relapses [4]. In our study, persistent bacteremia was found to be a risk factor for relapsing enterococcal IE. To the best of our knowledge, this is a novel finding. Persistent bacteremia

might be related to high initial bloodstream enterococcal inoculum, which may strongly depend on the source of the infection or the presence of intravascular devices, non-drained infectious foci and the type of initial antibiotic treatment, as well as to the characteristics of the bacterium. Persistent bacteremia, together with other recently identified potential risk factors for enterococcal IE relapses such as advanced liver disease [15] and genome modifications and phenotypic adaptation of changes of enterococcal strains [26] in *E. faecalis* IE, merit further investigation.

Treatment features

The length of antibiotic treatment was six weeks in median in both native and prosthetic valve enterococcal endocarditis. Among other determinants, this might reflect the high proportion of cases treated with double beta-lactam combination according to current guidelines [27,28], as well as the increasing complexity of enterococcal IE leading to six-week courses also for ampicillin plus gentamicin provided the average complication rates that likely precludes the use of shorter courses. Furthermore, lesser patients with enterococcal IE had indication and did indeed undergo cardiac surgery, and again this general observation only kept true for patients with prosthetic valve IE (less than a third of whom were operated) and not for native valve IE. Almost two thirds among the latter had indication for cardiac surgery while it was barely 50% among patients with prosthetic valve IE. The leading indication for cardiac surgery among native valve enterococcal IE was congestive heart failure and valve regurgitation; both of them were significantly more common in native than in prosthetic enterococcal IE.

Limitations

This study is constrained by several limitations. Firstly, we could not assess the epidemiological evolution of enterococcal IE along the study period because the database was still being updated with case report forms from cases of 2015 and 2016 sent by participating

centers. Secondly, EE cases were compared to the rest of the GAMES cohort IE cases instead of being compared only to oral and D-group streptococcal IE. However, our findings strongly suggest that the profile of EE is no longer similar to that of to the classical community-acquired streptococcal IE. Thirdly, due to a low proportion of cases including information of the antibiotic resistance profile of enterococci, we were not able to describe this aspect properly neither could we perform any analysis on the impact of high-level aminoglycoside resistance and vancomycin resistance on the prognosis of enterococcal IE. Fourthly, since most participating centers of the GAMES cohort are reference hospitals for cardiac surgery, the implications of a potential referral bias should be acknowledged. Fifth, the low number of non-*E. faecalis* enterococcal IE hampers the direct extrapolation of the results of the comparison between *E. faecalis* and non-*E. faecalis* IE. Finally, the long duration of the study period might represent a historical bias.

Conclusions

In conclusion, this study shows that enterococcal IE is an entity in constant evolution that constitutes the fourth common cause of IE in Spain. It affects mainly male and elderly patients with lots of comorbidities and prior episodes of IE; it is healthcare-associated in almost 50% of cases, involves prosthetic valves and entails heart failure and relapses more commonly than non-enterococcal IE. Although native enterococcal IE and non-enterococcal IE did not present significant differences on mortality rates, prosthetic valve enterococcal IE showed lower rates of in-hospital mortality and one-year mortality than non-enterococcal prosthetic IE. Relapses in enterococcal IE are associated to persistent bacteremia. Further studies investigating the relationship between relapses of enterococcal IE and potential contributing factors are warranted.

Perspectives

Competency in Medical Knowledge 1: Enterococcal endocarditis is changing epidemiologically while becoming increasingly frequent worldwide.

Competency in Medical Knowledge 2: Its clinical presentation is overall less severe than non-enterococcal endocarditis, yet it present higher rates of relapses and more frequently affects prosthetic valves.

Competency in Medical Knowledge 3: The outcomes of *Enterococcus faecalis* endocarditis (almost 90% of enterococcal endocarditis cases) are not significantly different from those of non-*E. faecalis* enterococcal endocarditis.

Competency in Patient Care: Enterococcal endocarditis should be suspected in elderly patients, especially in the healthcare setting. Follow-up after the initial admission is especially important due to an increased risk of relapses.

Translational Outlook: Future research might encompass a multidimensional inquiry on the characteristics of the bacterium, the host and medical and surgical management underlying the higher rates of relapses found among patients with enterococcal endocarditis.

References

1. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol. 2012;10:266-8.

2. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review. PLoS One. 2013;8:e82665.

3. Fernández Guerrero ML, Goyenechea A, Verdejo C, Roblas RF, de Górgolas M. Enterococcal endocarditis on native and prosthetic valves: a review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine (Baltimore). 2007;86:363-77.

4. Chirouze C, Athan E, Alla F, et al. Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. Clin Microbiol Infect. 2013;19:1140-7.

5. Muñoz P, Kestler M, De Alarcon A, et al. Current Epidemiology and Outcome of Infective Endocarditis: A Multicenter, Prospective, Cohort Study. Medicine (Baltimore) 2015; 94:e1816.

6. Olmos C, Vilacosta I, Fernández-Pérez C, et al. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). J Am Coll Cardiol. 2017;70:2795-804.

7. Regueiro A, Linke A, Latib A, et al. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. JAMA. 2016;316:1083-92.

8. Pericás JM, Zboromyrska Y, Cervera C, et al. Enterococcal endocarditis revisited. Future Microbiol. 2015;10:1215-40.

9. Megran DW. Enterococcal endocarditis. Clin Infect Dis. 1992;15:63-71.

10. Ambrosioni J, Hernandez-Meneses M, Téllez A, et al. The Changing Epidemiology of Infective Endocarditis in the Twenty-First Century. Curr Infect Dis Rep. 2017;19:21.

11. Arias CA, Panesso D, McGrath DM, et al. Genetic basis for in vivo daptomycin resistance in enterococci. N Engl J Med. 2011;365:892-900.

12. Gilmore MS, Clewell DB, Ike Y, Shankar N, editors. Enterococci: From Commensals to Leading Causes of Drug Resistant Infection [Internet]. Boston: Massachusetts Eye and Ear Infirmary; 2014-. Last accessed on October 2, 2018.

13. Fernández-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. Clin Infect Dis. 2013;56:1261-8.

14. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A Review of Combination Antimicrobial Therapy for Enterococcus faecalis Bloodstream Infections and Infective Endocarditis. Clin Infect Dis. 2018;67:303-9.

15. Pericàs JM, Cervera C, Moreno A, et al. Outcome of Enterococcus faecalis infective endocarditis according to the length of antibiotic therapy: Preliminary data from a cohort of 78 patients. PLoS One. 2018;13:e0192387.

16. Bouza E, Kestler M, Beca T, et al. The NOVA score: a proposal to reduce the need for transesophageal echocardiography in patients with enterococcal bacteremia. Clin Infect Dis. 2015;60:528-35.

17. Dahl A, Lauridsen TK, Arpi M, et al. Risk Factors of Endocarditis in Patients With Enterococcus faecalis Bacteremia: External Validation of the NOVA Score. Clin Infect Dis. 2016;63:771-5.

18. Berge A, Krantz A, Östlund H, Nauclér P, Rasmussen M. The DENOVA score efficiently identifies patients with monomicrobial Enterococcus faecalis bacteremia where echocardiography is not necessary. Infection. 2018 Sep 3.

19. Pericàs JM, Corredoira J, Moreno A, et al. Relationship Between Enterococcus faecalis Infective Endocarditis and Colorectal Neoplasm: Preliminary Results From a Cohort of 154 Patients. Rev Esp Cardiol (Engl Ed). 2017;70:451-8.

20. Pericàs JM, Corredoira J, Miró JM.Colorectal Adenomas. N Engl J Med. 2016;375:387-8.

21. Benito N, Miró JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. Ann Intern Med. 2009;150:586-94.

22. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30:633-8.

23. Durante-Mangoni E, Bradley S, Selton-Suty C, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med. 2008;168:2095-103.

24. Anderson DJ, Olaison L, McDonald JR, et al. Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the International Collaboration on Endocarditis-merged database. Eur J Clin Microbiol Infect Dis. 2005;24:665-70.

25. McDonald JR, Olaison L, Anderson DJ, et al. Enterococcal endocarditis: 107 cases from the international collaboration on endocarditis merged database. Am J Med. 2005;118:759-66.

26. Royer G, Melloul E, Roisin L, et al. Complete genome sequencing of Enterococcus faecalis strains suggests role of Ebp deletion in infective endocarditis relapse. Clin Microbiol Infect. 2019 Jul 12. pii: S1198-743X(19)30395-7. doi: 10.1016/j.cmi.2019.07.006.

27. Habib G, Lancellotti P, Antunes MJ, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36:3075-128.

404 28. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis,
405 Antimicrobial Therapy, and Management of Complications: A Scientific Statement for
406 Healthcare Professionals From the American Heart Association. Circulation 2015; 132:1435-
407 86.
408

Figure Legends

Central Illustration.

Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis.

(a) Kaplan-Meier curve for mortality at one year

(b) Kaplan-Meier curve for relapses over time.

436 **Table 1. Comparison of characteristics and outcome of enterococcal endocarditis and**
437 **endocarditis caused by other microorganisms from the GAMES Cohort (2008-2016).**

	Enterococcal IE (N=516)	**Non-enterococcal IE (N=3,308)**	***P***
Median age, years (IQR)	72 (64-78)	68 (55-77)	<0.001
Male sex (%)	357 (69.2%)	2206 (66.7%)	0.254
Comorbidities			
Diabetes mellitus	168 (32.6%)	913 (27.6%)	0.025
Chronic lung disease	139 (26.9%)	560 (16.9%)	<0.001
Ischemic cardiomyopathy	152 (29.5%)	841 (25.4%)	0.060
Congestive heart failure	197 (38.2%)	1077 (32.6%)	0.014
Moderate/severe liver disease	24 (4.7%)	144 (4.4%)	0.764
- Child Pugh score, mean (SD)	11 (2.83)	8.4 (2.46)	0.160
- MELD score, mean (SD)	20.6 (8.1)	19.7 (8.8)	0.733
Moderate/severe chronic renal failure	94 (18.2%)	489 (14.8%)	0.058
Hemodialysis	24 (4.7%)	157 (4.7%)	0.924
Neoplasm	94 (18.2%)	508 (15.4%)	0.114
Transplantation	9 (1.7%)	64 (1.9%)	0.760
Immunosuppressant therapy	38 (7.4%)	192 (5.8%)	0.201
IV drug use	5 (1%)	78 (2.4%)	0.006
HIV	4 (0.8%)	61 (1.8%)	0.018
Previous IE	63 (12.2%)	215 (6.5%)	<0.001
Congenital cardiac abnormality	5 (1%)	218 (6.6%)	<0.001

Non-congenital valve disease	252 (48.8%)	1431 (43.3%)	0.018
Median age-adjusted Charlson score (IQR)	5 (4-7)	4 (3-6)	<0.001
Type of endocarditis			
Native	324 (62.7%)	2007 (60.7%)	0.355
Prosthetic*	185 (35.8%)	955 (28.9%)	0.002
PCM/DF[+]	8 (1.5%)	346 (10.5%)	<0.001
Valve involvement[+]			
Aortic	332 (64.3%)	1545 (46.7%)	<0.001
Mitral	226 (43.8%)	1416 (42.8%)	0.672
Tricuspid	15 (2.9%)	186 (5.6%)	0.001
Pulmonary	0	51 (1.5%)	<0.001
Diagnosis of endocarditis according to modified Duke criteria			0.029
Definite	431 (83.5%)	2626 (79.4%)	
Possible	85 (16.5%)	682 (20.6%)	
Median time of symptoms duration until admission in non-nosocomial cases, days (IQR)	6.5 (1.3-22.8)	6.5 (2-18)	0.549
Source			
Oral	8 (1.6%)	220 (6.7%)	<0.001
Respiratory	2 (0.4%)	40 (1.2%)	0.096
Genitourinary	92 (17.8%)	106 (3.2%)	<0.001
Gastrointestinal	82 (15.9%)	172 (5.2%)	<0.001
Vascular	62 (12%)	637 (19.3%)	<0.001
Cutaneous	10 (1.9%)	260 (7.9%)	<0.001

Other	19 (3.8%)	202 (6.3%)	0.031
Unknown	262 (50.8%)	1708 (51.6%)	0.734
Etiology			NA
Enterococci *E. faecalis* *E. faecium* Other enterococci[±]	 468 (90.7%) 36 (7%) 12 (2.3%)	 - - -	
S. *aureus* MSSA MRSA	- - -	870 (26.3%) 849 97.6%) 21 (2.4%)	
Viridans group streptococci	-	616 (18.6%)	
Coagulase-negative staphylococci	-	664 (20.1%)	
Bovis group streptococci	-	244 (7.4%)	
Other streptococci	-	193 (5.8%)	
Other	-	711 (21.5%)[×]	
Acquisition			
Community	282 (54.7%)	1953 (59%)	0.062
Health-care associated Nosocomial Non-nosocomial health-care associated	219 (42.4%) 168 (32.6%) 51 (9.9%)	1229 (37.1%) 954 (28.8%) 275 (8.3%)	0.093 0.092 0.262
Unknown	15 (2.9%)	116 (3.5%)	0.486
Clinical complications			
New onset or worsening heart failure NYHA I	232 (45%) 12 (5.2%)	1270 (38.4%) 114 (9%)	0.005 0.054

NYHA II	35 (15.1%)	214 (16.9%)	0.506
NYHA III	95 (40.9%)	413 (32.5%)	0.013
NYHA IV	90 (38.8%)	529 (41.6%)	0.416
Persistent bacteremia	69 (13.4%)	378 (11.4%)	0.223
CNS emboli	86 (16.7%)	663 (20%)	0.058
Hemorrhagic	11 (12.8%)	110 (16.6%)	0.367
Extensive (>2cm)	0	109 (16.4%)	0.001
Multiple (>3)	6 (7%)	68 (10.3%)	0.337
Other major emboli	95 (18.4%)	687 (20.8%)	0.202
Pulmonary emboli	6 (1.2%)	183 (5.5%)	<0.001
Vertebral osteomyelitis	18 (3.5%)	97 (2.9%)	0.479
Non-vertebral osteomyelitis	6 (1.2%)	52 (1.6%)	0.536
Renal abscess	14 (2.7%)	87 (2.6%)	0.914
Splenic abscess	66 (12.8%)	310 (9.4%)	0.028
Heart conduction abnormality	39 (7.6%)	297 (9%)	0.262
Acute renal failure	191 (37%)	1177 (35.6%)	0.530
Septic shock	37 (7.2%)	432 (13.1%)	<0.001
Echocardiographic findings			
TEE performed	391 (75.8%)	2583 (78.1%)	0.253
Median ejection fraction (IQR)	60% (55-65)	60% (55-65)	0.536
Median vegetation size in mm (IQR)	8 (3-14)	8 (3-14)	0.088
Moderate-severe aortic regurgitation	193 (37.4%)	882 (26.7%)	<0.001
Moderate-severe mitral regurgitation	197 (38.2%)	1111 (33.6%)	0.048
Perivalvular abscess	62 (12%)	514 (15.5%)	0.024

Intracardiac fistula	4 (0.8%)	86 (2.6%)	<0.001
Pseudoaneurysm	18 (3.5%)	183 (5.5%)	0.023
Leaflet perforation/rupture	70 (13.6%)	436 (13.2%)	0.082
Treatment characteristics			
Antibiotics properly indicated	493 (95.5%)	3168 (95.8%)	0.817
Median length of antibiotic treatment, days (IQR)	42 (30-46)	36 (24-44)	<0.001
Cardiac surgery			
Indicated	316 (61.2%)	2182 (66%)	0.040
Operated during admission	210 (40.7%)	1520 (45.9%)	0.024
New surgery during the first year after admission	23 (4.5%)	144 (4.4%)	0.915
Outcomes			
In-hospital mortality	123 (23.8%)	892 (27%)	0.123
Mortality at 1-year	159 (30.8%)	1100 (33.3%)	0.266
Relapses	18 (3.5%)	57 (1.7%)	0.035

HIV: Human immunodeficiency syndrome; IQR: Interquartile range; MSSA: methicillin-susceptible *S. aureus;* MRSA: methicillin-resistant *S. aureus*; NA: not analyzed; PCM/DF: pacemakers/defibrillators

[*] There were 17 cases of endocarditis over TAVI, 3 of them occurring in the EE group and 14 in the NEE group (0.5% vs. 0.4%, P=0.802).

[+]Only episodes in which only PCM/DF are affected are included in this group. Episodes have been classified as native or prosthetic valve where a concomitant valve involvement exists.

The sum does not equal 100% because episodes with multivalve involvement are also counted.

[±] In 9 cases there was not identification at the species level (*Enterococcus spp*.), whereas the 3 remaining cases corresponded to one case of *E. durans, E. avium* and *E. gallinarum* each.

[×]Negative culture: 342 (48.1%); Gram negative bacilli: 163 (22.9%); Polymicrobial: 69 (9.7%); *Candida spp*: 64 (9.0%); Anaerobic bacteria: 39 (5.5%); Other fungi: 11 (1.5%); Miscellany: 23 (3.2%).

Table 2. Comparison of Health-Care acquired vs. Community-acquired Enterococcal Endocarditis.

	Community-acquired (N=282)	**Nosocomial-HCA (N=168)**	**Non-nosocomial HCA (N=51)**	***P***
Enterococcal species				0.342
E. faecalis	256 (90.8%)	153 (91.1%)	47 (92.2%)	
E. faecium	17 (6%)	15 (8.9%)	4 (7.8%)	
Other	9 (3.2%)*	0	0	
Median age, years (IQR)	73 (64-80)	73 (64-78)	71 (62-79)	0.332
Male sex (%)	195 (69.1%)	120 (71.4%)	31 (60.7%)	0.222
Comorbidities				
Diabetes mellitus	97 (34.4%)	46 (27.3%)	17 (33.3%)	0.296
Chronic lung disease	73 (25.9%)	49 (29.1%)	12 (23,5)	0.700
Ischemic cardiomyopathy	78 (27.7%)	56 (33.3%)	12 (23.5%)	0.285
Congestive heart failure	101 (35.8%)	74 (44%)	19 (37.2%)	0.221
Moderate/severe liver disease	8 (2.8%)	7 (4.2%)	8 (15.7%)	0.022
Moderate/severe chronic renal failure	43 (15.2%)	37 (22%)	12 (23.5%)	0.120
Hemodialysis	4 (1.4%)	11 (6.5%)	8 (15.6%)	<0.001
Neoplasm	49 (17.4%)	28 (16.6%)	13 (25.4%)	0.329
Transplantation	2 (0.7%)	6 (3.6%)	1 (2%)	0.806
Immunosuppressant therapy	15 (5.3%)	18 (10.7%)	4 (7.8%)	0.105
IV drug use	5 (1.8%)	0	0	0.024
HIV	4 (1.4%)	0	0	0.045

Previous IE	28 (9.9%)	24 (14.2%)	10 (19.6%)	0.101
Congenital cardiac abnormality	4 (1.4%)	2 (1.2%)	1 (2%)	0.918
Non-congenital valve disease	134 (47.5%)	89 (52.9%)	23 (45%)	0.445
Median age-adjusted Charlson score (IQR)	5 (4-7)	5 (4-7)	6 (4-8)	0.425
Type of endocarditis				
Native	192 (68.1%)	87 (51.7%)	37 (72.5%)	<0.001
Prosthetic	86 (30.5%)	79 (47%)	13 (25.4%)	<0.001
PCM/DF*	4 (1.4%)	3 (1.7%)	0	0.103
Valve involvement[+]				
Aortic	179 (63.5%)	105 (62.5%)	37 (72.5%)	0.403
Mitral	122 (43.3%)	75 (44.6%)	24 (47%)	0.868
Tricuspid	10 (3.5%)	4 (2.4%)	1 (2%)	0.398
Pulmonary	0	0	0	1.000
Clinical complications				
New onset or worsening heart failure	126 (44.7%)	78 (46.7%)	23 (45.1%)	0.849
Persistent bacteremia	36 (12.8%)	23 (13.7%)	8 (15.6%)	0.652
CNS emboli	43 (15.2%)	30 (17.8%)	10 (19.6%)	0.372
Other major emboli	57 (20.2%)	28 (16.7%)	6 (11.8%)	0.220
Pulmonary emboli	2 (0.7%)	4 (2.3%)	0	0.280
Vertebral osteomyelitis	9 (3.2%)	7 (4.1%)	2 (3.9%)	0.779
Non-vertebral osteomyelitis	5 (1.8%)	0	1 (1.9%)	0.152
Renal abscess	8 (2.8%)	0	0	0.695
Splenic abscess	40 (14.2%)	6 (3.5%)	3 (5.8%)	<0.001
Heart conduction abnormality	22 (7.8%)	12 (7.1%)	3 (5.8%)	0.880

Acute renal failure	112 (39.7%)	51 (30.3%)	19 (37.2%)	0.134
Septic shock	19 (6.7%)	14 (8.3%)	3 (5.8%)	0.761
Echocardiographic findings				
TEE performed	206 (73%)	134 (79.8%)	40 (78.4%)	0.093
Median ejection fraction (%, IQR)	60 (55-65)	60 (50-65)	60 (50-68)	0.465
Median vegetation size (mm, IQR)	8 (3-15)	10 (7-19)	10.5 (8-13)	0.729
Moderate-severe aortic regurgitation	107 (37.9%)	54 (32.1%)	24 (47%)	0.133
Moderate-severe mitral regurgitation	119 (42.2%)	49 (29.1%)	25 (49%)	0.006
Perivalvular abscess	23 (8.2%)	28 (16.6%)	9 (17.6%)	0.011
Intracardiac fistula	2 (0.7%)	2 (1.2%)	0	0.235
Pseudoaneurysm	5 (1.8%)	6 (3.6%)	5 (9.8%)	0.010
Leaflet perforation/rupture	44 (15.6%)	19 (11.3%)	6 (11.7%)	0.163
Treatment characteristics				
Median length of antibiotic treatment, days (IQR)	42 (29-46)	42 (33-47)	42 (28-46)	0.317
Cardiac surgery	121 (42.9%)	57 (33.9%)	23 (45.1%)	0.127
Outcomes				
In-hospital mortality	60 (21.3%)	45 (25.5%)	16 (31.3%)	0.186
One-year mortality	79 (28%)	53 (31.5%)	22 (43.1%)	0.094
Relapses[±]	10 (3.5%)	3 (1.7%)	4 (7.8%)	0.109

455 [*] 8 cases due to *Enterococcus spp*. and 1 case of *E. durans* IE

456 [±] One case of relapse among EE was not included because it had an unknown source of
457 acquisition.

458

459 **Table 3. Comparison of *E. faecalis* vs. non-*E. faecalis* Enterococcal Endocarditis**

	***E. faecalis* IE (N=468)**	***Non-E. faecalis* IE (N=48)**	***P***
Median age, years (IQR)	73 (64.5-79)	68.5 (59.5-76)	0.080
Male sex (%)	325 (69.4%)	32 (66.7%)	0.697
Comorbidities			
Diabetes mellitus	151 (32.3%)	17 (35.4%)	0.663
Chronic lung disease	130 (27.8%)	9 (18.8%)	0.133
Ischemic cardiomyopathy	140 (29.9%)	12 (25%)	0.457
Congestive heart failure	187 (40%)	10 (20.8%)	0.002
Moderate/severe liver disease	20 (4.3%)	4 (8.3%)	0.322
Moderate/severe chronic renal failure	88 (18.8%)	6 (12.5%)	0.217
Hemodialysis	24 (5.1%)	0	<0.001
Neoplasm	81 (17.3%)	13 (27.1%)	0.142
Transplantation	8 (1.7%)	1 (2.1%)	0.862
Immunosuppressant therapy	33 (7.1%)	5 (10.4%)	0.461
IV drug use	4 (0.9%)	1 (2.1%)	0.560
HIV	3 (0.6%)	1 (2.1%)	0.491
Previous IE	57 (12.2%)	6 (12.5%)	0.949
Congenital cardiac abnormality	6 (1.3%)	1 (2.1%)	0.706
Non-congenital valve disease	229 (48.9%)	23 (47.9%)	0.893
Median age-adjusted Charlson score (IQR)	5 (4-7)	5 (3-7)	0.227
Type of endocarditis			
Native	287 (61.3%)	37 (77.1%)	0.015
Prosthetic	174 (37.2%)	11 (22.9%)	0.028
PCM/DF*	7 (1.5%)	0	0.109

Valve involvement[+]			
Aortic	302 (64.5%)	30 (62.5%)	0.782
Mitral	203 (43.4%)	23 (47.9%)	0.549
Tricuspid	14 (3%)	1 (2.1%)	0.681
Pulmonary	0	0	1.000
Acquisition			
Community	256 (54.7%)	26 (54.2%)	0.944
Health-care associated	197 (42.1%)	22 (45.8%)	0.617
Nosocomial	153 (32.7%)	15 (31.3%)	0.838
Non-nosocomial health-care associated	44 (9.4%)	7 (14.6%)	0.326
Unknown	15 (3.2%)	0	0.124
Clinical complications			
New onset or worsening heart failure	214 (45.7%)	18 (37.5%)	0.264
Persistent bacteremia	61 (13%)	8 (16.7)	0.517
CNS emboli	75 (16%)	11 (22.9%)	0.274
Other major emboli	85 (18.2%)	10 (20.8%)	0.663
Pulmonary emboli	4 (0.9%)	2 (4.2%)	0.256
Vertebral osteomyelitis	17 (3.6%)	1 (2.1%)	0.577
Non-vertebral osteomyelitis	6 (1.3%)	0	0.358
Renal abscess	12 (2.6%)	2 (4.2%)	0.590
Splenic abscess	60 (12.8%)	6 (12.5%)	0.949
Heart conduction abnormality	36 (7.7%)	3 (6.3%)	0.697
Acute renal failure	172 (36.8%)	19 (39.6%)	0.702
Septic shock	31 (6.6%)	6 (12.5%)	0.232
Echocardiographic findings			
TEE performed	358 (76.5%)	33 (68.8%)	0.267
Median ejection fraction (IQR)	60 (55-66)	60 (55-65)	0.805

Median vegetation size, mm (IQR)	8 (3-14)	6 (3-8)	0.110
Moderate-severe aortic regurgitation	179 (38.2%)	14 (29.2%)	0.191
Moderate-severe mitral regurgitation	183 (39.1%)	14 (209.2%)	0.153
Paravalvular abscess	60 (12.8%)	2 (4.2%)	0.008
Intracardiac fistula	3 (0.6%)	1 (2.1%)	0.491
Pseudoaneurysm	16 (3.4%)	2 (4.2%)	0.803
Leaflet perforation/rupture	63 (13.5%)	7 (14.6%)	0.585
Treatment characteristics			
Median length of antibiotic treatment, days (IQR)	42 (30-46)	42 (28-44)	0.389
Cardiac surgery	192 (41%)	18 (37.5%)	0.632
Initial antibiotic treatment			
Double beta-lactam combination	318 (67.9%)	11 (22.9%)	<0.001
Beta-lactam plus aminoglycoside	96 (20.3%)	5 (10.4%)	0.092
Other	54 (11.4%)[±]	32 (66.7%)	<0.001
Outcomes			
In-hospital mortality	109 (23.3%)	14 (29.2%)	0.391
Mortality at 1-year	144 (30.8%)	15 (31.3%)	0.945
Relapses	16 (3.4%)	2 (4.2%)	0.803

± Vancomycin plus aminoglycoside: 11 (20.4%); Vancomycin plus other: 8 (14.8%); Daptomycin: 7 (13%); Daptomycin plus beta-lactam: 5 (9.3%); Daptomycin plus fosfomycin: 1 (1.8%); Beta-lactam alone: 7 (13%); Beta-lactam plus quinolone: 4 (7.4%); Linezolid: 2 (3.7%); Other: 9 (16.7%).

Table 4. Analysis of Risk Factors for In-Hospital Mortality, One-year Mortality and Relapses for 516 cases of Enterococcal Endocarditis.

	One-Year Mortality				Relapses			
	Univariate		***Multivariate***		***Univariate***		***Multivariate***	
	HR (95%CI)	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
E. faecalis	0.99 (0.58, 1.68)	0.970			0.71 (0.16, 3.14)	0.663		
Initial antibiotic treatment included gentamicin	N.A.				N.A.			
Male sex	0.94 (0.67, 1.31)	0.722			0.44 (0.16, 1.17)	0.103	0.50 (0.19, 1.36)	0.174
Age (years)	1.00 (0.99, 1.01)	0.534			1.02 (0.98, 1.07)	0.322		
Diabetes mellitus	1.56 (1.14, 2.14)	0.006	1.00 (0.63, 1.62)	0.972	0.69 (0.22, 2.14)	0.524		
Congestive heart failure	1.10 (0.80, 1.51)	0.561			0.98 (0.36, 2.70)	0.976		
Moderate-severe chronic renal failure	1.97 (1.40, 2.79)	<0.001			1.05 (0.30, 3.67)	0.943		
Moderate-severe liver disease	2.58 (2.52, 4.40)	<0.001	2.62 (1.31, 5.24)	0.007	2.95 (0.67, 12.96)	0.152	2.03 (0.45, 9.16)	0.351

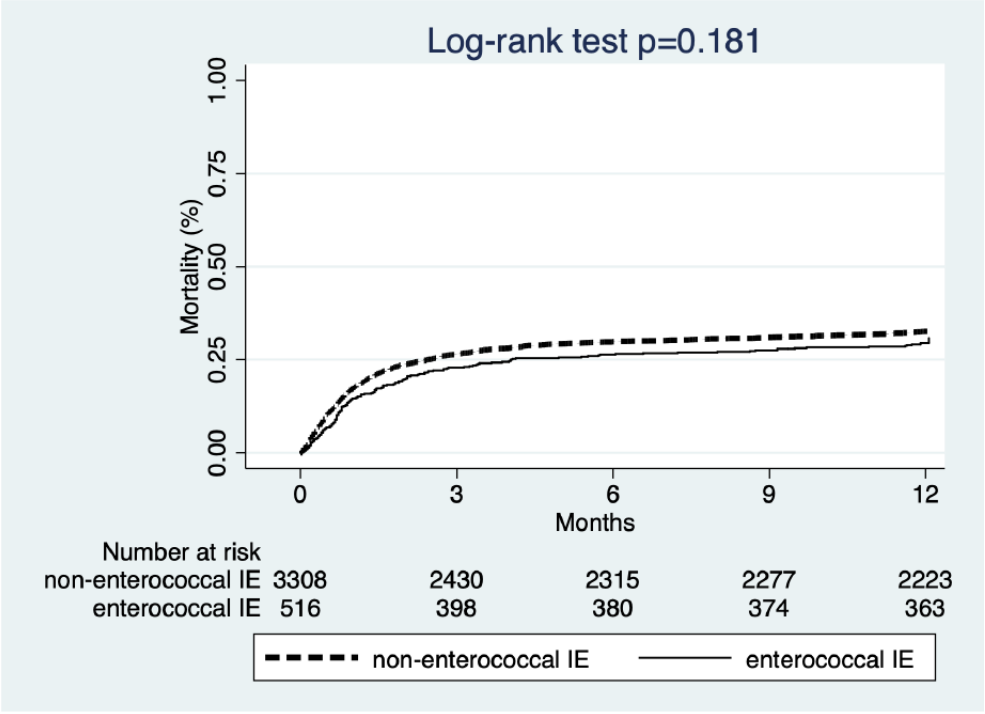
Previous IE	0.53 (0.30, 0.96)	0.041	0.42 (0.21, 0.84)	0.012	2.45 (0.79, 7.59)	0.124		
Age-adjusted Charlson score	1.16 (1.10, 1.23)	<0.001	1.12 (1.01, 1.24)	0.010	0.93 (0.76, 1.14)	0.497		
Community acquisition	0.79 (0.58, 1.08)	0.154			1.17 (0.42, 3.29)	0.765		
Prosthetic IE	0.78 (0.56, 1.09)	0.158			1.82 (0.68, 4.85)	0.232		
Urinary source	1.31 (0.89, 1.91)	0.172			0.65 (0.15, 2.85)	0.576		
Aortic valve IE	1.08 (0.78, 1.50)	0.623			0.42 (0.16, 1.14)	0.094	0.42 (0.16, 1.15)	0.095
Mitral valve IE	1.07 (0.79, 1.48)	0.602			2.15 (0.78, 5.92)	0.133	1.67 (0.49, 5.78)	0.412
Paravalvular complications*	1.52 (1.09, 2.12)	0.014	1.87 (1.22, 2.87)	0.040	0.19 (0.03, 1.43)	0.115	0.22 (0.03, 1.73)	0.153
Vegetation size ≥ 10mm	0.79 (0.46, 1.37)	0.414			0.96 (0.16, 5.72)	0.961		
New onset heart failure	2.37 (1.72, 3.27)	<0.001	2.42 (1.53, 3.83)	<0.001	0.94 (0.35, 2.52)	0.904		

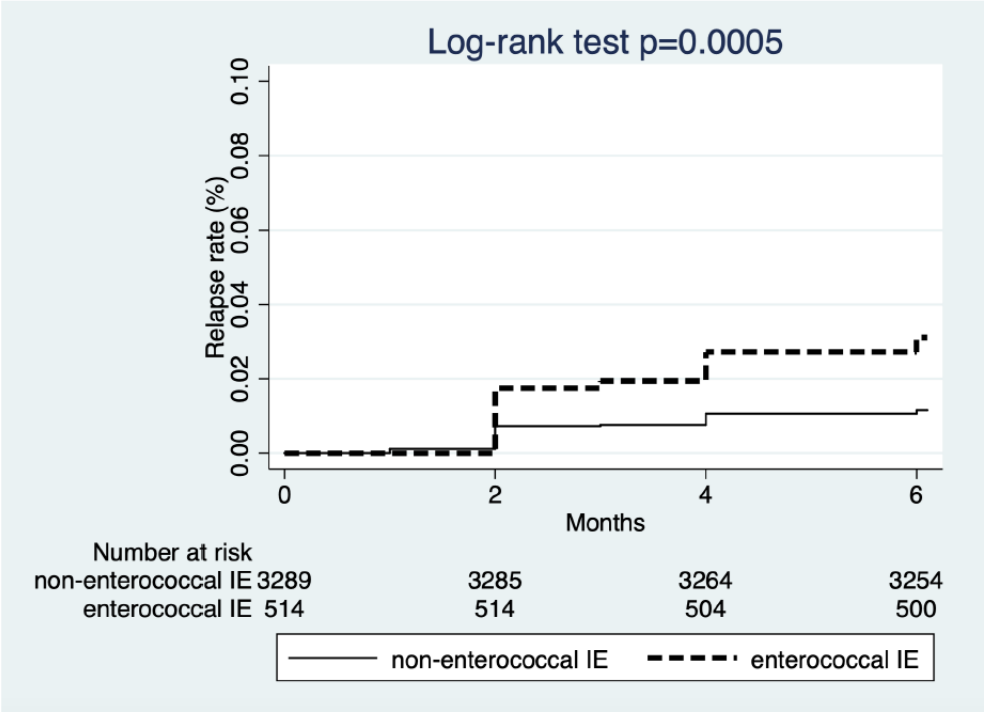
Persistent bacteremia	1.37 (0.90, 2.07)	0.143			3.99 (1.45, 10.98)	0.007	4.03 (1.43, 11.33)	0.008
CNS emboli	1.23 (0.83, 1.83)	0.313			1.12 (0.32, 3.94)	0.852		
Other emboli	1.05 (0.71, 1.57)	0.787			0.99 (0.28, 3.48)	0.993		
New heart conduction abnormality	1.58 (0.94, 2.66)	0.082			N.A.			
Acute renal failure	1.86 (1.36, 2.54)	<0.001	1.30 (0.84, 2.00)	0.241	1.31 (0.49, 3.52)	0.589		
Septic shock	3.09 (1.99, 4.77	<0.001	1.76 (1.04, 2.99)	0.033	N.A.			
Inappropriate initial antibiotics	1.71 (0.90, 3.25)	0.102			N.A.			
Cardiac surgery	0.62 (0.45, 0.87)	0.006	0.88 (0.54, 1.43)	0.613	0.33 (0.09, 1.15)	0.083	0.48 (0.13, 1.71)	0.253
Logistic EuroSCORE	1.02 (1.01, 1.03	<0.001	1.02 (1.01, 1.03)	0.002	1.00 (0.98, 1.03)	0.923		

467 * Paravalvular complications include at least one of the following: periannular abscess, pseudoaneurysm, fistula, or leaflet perforation/rupture.

468 N.A.= Non-assessed due to low number of events

Central Illustration. Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis. (a) Kaplan-Meier curve for mortality at one year; (b) Kaplan-Meier curve for relapses over time.





Clinical areas and patient features in which enterococcal endocarditis is of special relevance:

- Elderly patients
- TAVI*
- Prosthetic valve endocarditis
- Degenerative left-sided valve disease
- Aortic involvement
- Chronic lung disease
- Chronic heart failure
- Hemodialysis*****

* Shown in other large series

Title: A contemporary picture of enterococcal endocarditis: prospective study of 516 cases from the GAMES Cohort

Short Title: Prognostic factors of enterococcal endocarditis

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Abstract

Background: Enterococcal endocarditis (EE) is a growing entity in Western countries. However, quality data from large studies is lacking.
Objectives: To describe the characteristics and analyze the prognostic factors of EE in the GAMES cohort.
Methods: Post-hoc analysis of a prospectively collected cohort of patients from 35 Spanish centers from 2008 to 2016. Characteristics and outcomes of 516 cases of EE were compared to those of 3,308 cases of non-enterococcal endocarditis (NEE). Logistic regression and Cox proportional hazards regression analysis were performed to investigate risk factors for in-hospital and one-year mortality, and relapses.
Results: Patients with EE were significantly older, presented more frequently chronic lung disease, chronic heart failure, prior endocarditis, degenerative valve disease and had higher median age-adjusted Charlson score. EE more frequently involved the aortic valve and prosthesis (64.3% vs. 46.7%; P<0.001; and 35.9% vs. 28.9%; P=0.002, respectively) but less frequently pacemakers/defibrillators (1.5% vs. 10.5%; P<0.001), and showed higher rates of acute heart failure (45% vs. 38.3%;P=0.005). Cardiac surgery was less frequently performed in EE (40.7% vs.45.9%;P=0.024). No differences in in-hospital mortality and one-year mortality were found, whereas relapses were significantly higher in EE (3.5% vs. 1.7%; P=0.035). Increasing Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications were risk factors for mortality, whereas prior endocarditis was protective and persistent bacteremia constituted the sole risk factor for relapse.
Conclusions: Besides other baseline and clinical differences, EE more frequently affects prosthetic valves and less frequently pacemakers/defibrillators. EE presents higher rates of relapse than NEE.

Condensed abstract: Enterococcal endocarditis (EE) is a growing issue in Western countries. By comparing 516 cases of EE with 3,308 cases of NEE, we found older median age and higher comorbidity rates among EE than in NEE, as well as higher rates of aortic valve and prosthetic valve involvement, and heart failure. Mortality did not significantly differ between EE and NEE, whereas relapses were higher in EE. Risk factors for mortality in EE were Charlson score, LogEuroSCORE, acute heart failure, septic shock and paravalvular complications, whereas persistent bacteremia was associated with a higher likelihood of relapses.

Keywords: Infective endocarditis, enterococci, heart failure, relapses, prosthetic valves, epidemiology.

Abbreviations: CNS, central nervous system; EE, enterococcal endocarditis; HCA, healthcare-associated; IE, infective endocarditis; MRSA, methicillin-resistant *S. aureus*; NEE, non-enterococcal endocarditis; PCM/DF, pacemakers/defibrillators; TAVI, transaortic valve implantation; TEE, transesophageal echocardiography

Introduction

Enterococci have been identified as a growing pathogen, primarily in health-care associated infections in the U.S., where vancomycin-resistant strains pose a serious challenge to the health system [1]. However, enterococci are also playing an increasingly important role in infective endocarditis (IE) [2], with most recent series placing it as the third leading causative agent in high-income countries, reaching up to 15-20% of total cases [3-6]. Moreover, enterococci are the leading causative agent of transaortic valve implants (TAVI)-associated IE [7].

Most cases (around 90%) of enterococcal IE are caused by *E. faecalis* [8]. Since the turn of the 21st century, the classically described clinical presentation of enterococcal IE as a community-acquired, subacute pauci-symptomatic disease of genitourinary source [10] is progressively turning in a more aggressive, acute, more frequently healthcare-associated (HCA) disease of occurring predominantly amongst elderly patients with a large burden of comorbidities and seldom a clear identifiable source. [9,10].

The focus of recent relevant studies addressing enterococcal IE is largely placed on the genetic and molecular aspects [11,12], impact of antimicrobial resistance (e.g. vancomycin, high-level aminoglycoside resistance and daptomycin resistance) [1,8,11,12], therapeutic options [13-15] or the use of TEE to detect IE [16-18], whereas there is a relative paucity of studies explaining the main clinical and epidemiological changes of enterococcal IE in the last two decades and their underlying mechanisms, such as its potential association with colorectal neoplasms [19,20].

We aimed to investigate the main characteristics of enterococcal IE in a cohort of 516 patients prospectively collected from 2008 to 2016 and to compare them with those of non-enterococcal IE.

Methods

Design: multicenter prospective observational study including 35 Spanish centers between 2008 and 2016. The characteristics of the GAMES cohort, collection of data variables through a specific central registration depository, and definitions are described elsewhere [5]. The work-up for searching potential sources of the infection, including gastrointestinal tract screening, was not systematic but was decided by the treating physician. Persistent bacteremia was defined as positive blood cultures beyond seven days of effective antibiotic therapy; relapse refers to a new episode of IE due to the same microorganism within the next 6 months after the initial episode; acute renal failure was defined in the data collection sheet as a worsening equal or higher than 25% of serum creatinine or glomerular clearance occurring within a lapse of 72h; community-acquired IE was defined as IE diagnosed within the first 48 hours of admission in a patient who did not fulfill the criteria for HCA infection. HCA infection encompasses nosocomial and non-nosocomial HCA IE [21]. Nosocomial IE was defined as IE in a patient who had been hospitalized for >48 hours before the onset of signs or symptoms consistent with IE. Non-nosocomial HCA IE was an IE diagnosed within 48 hours of admission of an outpatient.

Patients: adult individuals with definite or possible IE diagnosed according to the modified Duke criteria [22].

Outcomes: in-hospital and one-year mortality (death due to any causes within 30 days and 365 days from the admission, respectively), and relapses.

Statistical analysis: Categorical variables were summarized as percentages and continuous variables as means and standard deviations. Categorical variables were compared using the chi-square test (or Fisher's exact test where necessary). Continuous variables were compared using the Kruskal-Wallis test. Cox proportional hazards regression analysis was utilized to investigate risk factors for one-year mortality and relapses. Variables with $P<0.20$ in the

univariate analysis were included in the models. Kaplan-Meier survival curves free of mortality at one year and relapses were generated with log-rank test analysis and considering censored episodes according to the time measured for each endpoint. A two-sided $P<0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Patients with enterococcal IE were significantly older and had higher rates of comorbidities, leading to a significantly higher median age-adjusted Charlson score (**Table 1**). Diabetes mellitus, chronic lung disease, congestive heart failure, previous IE, and non-congenital valve disease were all significantly more frequent among enterococcal IE, whereas ischemic cardiomyopathy and chronic renal failure, although more frequent too among enterococcal IE, did not reach statistical significance. On the other hand, iv drug use, HIV infection and congenital heart abnormalities were significantly more common among patients with non-enterococcal IE. The proportion of prosthetic valve IE was significantly higher in the enterococcal IE group, whereas PCM/DF-associated IE was significantly more frequent in the non-enterococcal IE group. The aortic valve was significantly more frequently involved in enterococcal IE cases, while the tricuspid and pulmonary valve were more commonly affected in non-enterococcal IE. Around half of the cases in both groups had an unknown source of the infection. The median time elapsed between the appearance of symptoms and hospital admission was not different between the two groups. Genitourinary and gastrointestinal foci were significantly more common among enterococcal IE episodes; meanwhile, oral, vascular and cutaneous sources were significantly more frequent in the non-enterococcal IE group. *E. faecalis* caused 90.7% of cases in the enterococcal IE group, being *S. aureus*, coagulase-negative staphylococci, and viridans group streptococci the more frequent causative agents in the non-enterococcal IE group. As for the proportion of cases from the global cohort, *S. aureus* represented 22.8%, coagulase-negative staphylococci 17.4%, viridans group streptococci 16.1%, enterococci 13.5%, Bovis group streptococci 6.4% and other streptococci 5%. Enterococci accounted for 9.5% of cases in patients aged less than 65 years and 16.4% among patients ≥65 years old (P<0.001). There were no cases of enterococcal IE caused by vancomycin-resistant enterococci. The site of acquisition did not

significantly differ between the two groups. Clinically, non-enterococcal IE presented with significantly higher rates of extensive CNS emboli, pulmonary emboli, and septic shock, as well as perivalvular abscesses, intracardiac fistula and pseudoaneurysm in the echocardiography, whereas enterococcal IE presented significantly higher rates of new onset heart failure and splenic abscesses. Enterococcal IE received a significantly longer median time of antibiotic therapy (42 vs. 36 days; P<0.001), being rates of cardiac surgery higher among non-enterococcal IE patients. Remarkably, 8 patients in the enterococcal IE group did not undergo cardiac surgery when indicated due to advanced liver disease, whereas this happened in 21 patients in the non-enterococcal group (1.5% vs. 0.6%; P=0.025, not shown). In-hospital and one-year mortality did not differ between both groups, yet relapses were significantly higher among patients with enterococcal IE.

The characteristics and outcomes of enterococcal and non-enterococcal IE are compared in the Supplementary material among native valve IE cases (**Supplementary Table 1**), prosthetic valve IE cases (**Supplementary Table 2**) and patients undergoing cardiac surgery (**Supplementary Table 3**). Notably, both in-hospital and one-year mortality were significantly higher among patients with non-enterococcal prosthetic valve IE, whereas relapses were significantly higher among patients with enterococcal prosthetic valve IE.

A comparison of HCA vs. community-acquired enterococcal IE cases is shown in **Table 2**. Notably, HCA enterococcal cases more frequently involved prosthetic valves and had higher rates of chronic liver and renal disease, including dialysis, and transplantation, and immunosuppres therapy, whereas community-acquired enterococcal IE involved native valves significantly more frequently and presented higher rates of iv drug use and HIV infection. Outcomes did not significantly differ between the two groups.

The characteristics and outcomes of enterococcal IE caused by *E. faecalis* are compared to those enterococcal IE cases caused by other species in **Table 3**. Of note, patients with *E.*

198 *faecalis* IE showed a trend to elder ages and presented significantly higher rates of chronic
199 congestive heart failure, chronic dialysis, prosthetic valve IE, and paravalvular abscess.
200 Patients with *E. faecalis* IE significantly received as initial antibiotic treatment double beta-
201 lactam combinations, whereas there were no differences between groups associated with
202 beta-lactam plus aminoglycoside initial combinations. Non-*E. faecalis* IE was more
203 frequently treated with other type of antibiotic treatment, being vancomycin combined with
204 an aminoglycoside the third most common combination among *E. faecalis* IE patients. Ten
205 (62.5%) of the 16 relapses occurring in patients with *E. faecalis* IE had received double beta-
206 lactam therapy, 5 (31.2%) received beta-lactam plus aminoglycosides and 1 (6.3%)
207 vancomycin plus gentamicin. The two relapses occurring in non-*E.faecalis* IE patients had
208 received other type of combinations. Outcomes did not significantly differ between the two
209 groups.
210 In the multivariate analysis, increasing age-adjusted Charlson score, paravalvular
211 complications, new onset of heart failure, septic shock and logistic EuroSCORE were
212 identified as risk factors for one-year mortality and prior episode of IE was protective.
213 Persistent bacteremia was identified as a risk factor for relapse (**Table 4**). Curves for mortality
214 and relapse over time are shown in the **Central Illustration**.
215
216

Discussion

Epidemiology and main clinical characteristics

Ours is the largest national series of enterococcal IE described to date. In terms of epidemiological findings, this study confirms some of the common traits of the enterococcal IE profile described in studies conducted during the last fifteen years, but we also found some differences in this regard. Remarkably, as foreseen in the previous literature, median age, female sex, comorbidities, unknown source of infection and healthcare acquisition among enterococcal IE cases are on the rise. For example, Chirouze et al provided data on 500 cases of enterococcal IE from the International Collaboration on Endocarditis (ICE) collected from 2000 to 2006 and compared them with 823 cases of IE caused by oral streptococci and 293 cases of D group streptococcal IE [4]. North America was the region where more cases of enterococcal IE came from (50%), 90.6% of cases were caused by *E. faecalis*, median age was 65 years, 72.6% of cases occurred in men, 22.4% had diabetes, 8.4% were on chronic hemodialysis, 11.2% had cancer, 12.5% of cases had a prior episode of IE, 23.4% of cases overall were healthcare-associated and enterococcal IE involved prosthetic valves (in 29.1% of cases) significantly more frequently than streptococcal IE [4]. As in the case of another study from the ICE [23], we found that enterococcal IE is significantly more frequent among patients aged 65 years or more. By comparing to all other etiologies of IE, we have also identified that enterococcal IE is significantly less frequent among iv drug users, people living with HIV, patients with congenital heart disease, whereas it significantly more often the aortic valve and affected people with chronic diseases such as respiratory diseases, ischemic myocardiopathy, chronic heart failure, chronic renal disease or degenerative valve disease.

From a clinical standpoint, the two major findings of our study are the high rate of prosthetic valve involvement and heart failure. In addition, we found that in spite of presenting very

similar profiles in all other aspects, *E. faecalis* produced significantly more prosthetic valve IE cases than other enterococcal species while the latter produced significantly more native valve IE, which has not been noted before.

Complications and outcome

Heart failure was a prognostic factor for mortality among patients with EE. However, when analyzing native and prosthetic valve IE separately, we did not find higher heart failure rates in prosthetic enterococcal IE. Heart failure as a common trait of enterococcal IE has previously been defined in some reports [24,25] but remarkably not in the Chirouze et al study [4]. In our cohort of enterococcal IE, we also find higher rates of moderate-severe aortic and mitral regurgitation than in other types of IE. We hypothesize this might be due to the higher frequency of heart abnormalities of elderly patients rather than to a special ability for valve tissue destruction inherent to enterococci, which is consistent with the lower rates of paravalvular complications we observed among patients with enterococcal IE and the fact than the median time elapsed from the onset of symptoms to admission was not different between enterococcal and non-enterococcal IE.

Whereas we did not find significant differences in in-hospital and one-year mortality between enterococcal and non-enterococcal IE overall, both were significantly lower in enterococcal prosthetic valve IE than in non-enterococcal prosthetic valve IE in spite of the aforementioned lower rates of cardiac surgery.

Although enterococcal IE classically presents with higher rates of relapse than other types of IE [8], the risk factors associated with this phenomenon have been scarcely investigated to date. Moreover, no other large study on enterococcal IE had previously confirmed a significantly higher rate, including the ICE study led by Chirouze, which did not provide data on relapses [4]. In our study, persistent bacteremia was found to be a risk factor for relapsing enterococcal IE. To the best of our knowledge, this is a novel finding. Persistent bacteremia

might be related to high initial bloodstream enterococcal inoculum, which may strongly depend on the source of the infection or the presence of intravascular devices, non-drained infectious foci and the type of initial antibiotic treatment, as well as to the characteristics of the bacterium. Persistent bacteremia, together with other recently identified potential risk factors for enterococcal IE relapses such as advanced liver disease [15] and genome modifications and phenotypic adaptation of changes of enterococcal strains [26] in *E. faecalis* IE, merit further investigation.

Treatment features

The length of antibiotic treatment was six weeks in median in both native and prosthetic valve enterococcal endocarditis. Among other determinants, this might reflect the high proportion of cases treated with double beta-lactam combination according to current guidelines [27,28], as well as the increasing complexity of enterococcal IE leading to six-week courses also for ampicillin plus gentamicin provided the average complication rates that likely precludes the use of shorter courses. Furthermore, lesser patients with enterococcal IE had indication and did indeed undergo cardiac surgery, and again this general observation only kept true for patients with prosthetic valve IE (less than a third of whom were operated) and not for native valve IE. Almost two thirds among the latter had indication for cardiac surgery while it was barely 50% among patients with prosthetic valve IE. The leading indication for cardiac surgery among native valve enterococcal IE was congestive heart failure and valve regurgitation; both of them were significantly more common in native than in prosthetic enterococcal IE.

Limitations

This study is constrained by several limitations. Firstly, we could not assess the epidemiological evolution of enterococcal IE along the study period because the database was still being updated with case report forms from cases of 2015 and 2016 sent by participating

centers. Secondly, EE cases were compared to the rest of the GAMES cohort IE cases instead of being compared only to oral and D-group streptococcal IE. However, our findings strongly suggest that the profile of EE is no longer similar to that of to the classical community-acquired streptococcal IE. Thirdly, due to a low proportion of cases including information of the antibiotic resistance profile of enterococci, we were not able to describe this aspect properly neither could we perform any analysis on the impact of high-level aminoglycoside resistance and vancomycin resistance on the prognosis of enterococcal IE. Fourthly, since most participating centers of the GAMES cohort are reference hospitals for cardiac surgery, the implications of a potential referral bias should be acknowledged. Fifth, the low number of non-*E. faecalis* enterococcal IE hampers the direct extrapolation of the results of the comparison between *E. faecalis* and non-*E. faecalis* IE. Finally, the long duration of the study period might represent a historical bias.

Conclusions

In conclusion, this study shows that enterococcal IE is an entity in constant evolution that constitutes the fourth common cause of IE in Spain. It affects mainly male and elderly patients with lots of comorbidities and prior episodes of IE; it is healthcare-associated in almost 50% of cases, involves prosthetic valves and entails heart failure and relapses more commonly than non-enterococcal IE. Although native enterococcal IE and non-enterococcal IE did not present significant differences on mortality rates, prosthetic valve enterococcal IE showed lower rates of in-hospital mortality and one-year mortality than non-enterococcal prosthetic IE. Relapses in enterococcal IE are associated to persistent bacteremia. Further studies investigating the relationship between relapses of enterococcal IE and potential contributing factors are warranted.

Perspectives

Competency in Medical Knowledge 1: Enterococcal endocarditis is changing epidemiologically while becoming increasingly frequent worldwide.

Competency in Medical Knowledge 2: Its clinical presentation is overall less severe than non-enterococcal endocarditis, yet it present higher rates of relapses and more frequently affects prosthetic valves.

Competency in Medical Knowledge 3: The outcomes of *Enterococcus faecalis* endocarditis (almost 90% of enterococcal endocarditis cases) are not significantly different from those of non-*E. faecalis* enterococcal endocarditis.

Competency in Patient Care: Enterococcal endocarditis should be suspected in elderly patients, especially in the healthcare setting. Follow-up after the initial admission is especially important due to an increased risk of relapses.

Translational Outlook: Future research might encompass a multidimensional inquiry on the characteristics of the bacterium, the host and medical and surgical management underlying the higher rates of relapses found among patients with enterococcal endocarditis.

References

1. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol. 2012;10:266-8.

2. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review. PLoS One. 2013;8:e82665.

3. Fernández Guerrero ML, Goyenechea A, Verdejo C, Roblas RF, de Górgolas M. Enterococcal endocarditis on native and prosthetic valves: a review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. Medicine (Baltimore). 2007;86:363-77.

4. Chirouze C, Athan E, Alla F, et al. Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. Clin Microbiol Infect. 2013;19:1140-7.

5. Muñoz P, Kestler M, De Alarcon A, et al. Current Epidemiology and Outcome of Infective Endocarditis: A Multicenter, Prospective, Cohort Study. Medicine (Baltimore) 2015; 94:e1816.

6. Olmos C, Vilacosta I, Fernández-Pérez C, et al. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). J Am Coll Cardiol. 2017;70:2795-804.

7. Regueiro A, Linke A, Latib A, et al. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. JAMA. 2016;316:1083-92.

8. Pericás JM, Zboromyrska Y, Cervera C, et al. Enterococcal endocarditis revisited. Future Microbiol. 2015;10:1215-40.

9. Megran DW. Enterococcal endocarditis. Clin Infect Dis. 1992;15:63-71.

10. Ambrosioni J, Hernandez-Meneses M, Téllez A, et al. The Changing Epidemiology of Infective Endocarditis in the Twenty-First Century. Curr Infect Dis Rep. 2017;19:21.

11. Arias CA, Panesso D, McGrath DM, et al. Genetic basis for in vivo daptomycin resistance in enterococci. N Engl J Med. 2011;365:892-900.

12. Gilmore MS, Clewell DB, Ike Y, Shankar N, editors. Enterococci: From Commensals to Leading Causes of Drug Resistant Infection [Internet]. Boston: Massachusetts Eye and Ear Infirmary; 2014-. Last accessed on October 2, 2018.

13. Fernández-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. Clin Infect Dis. 2013;56:1261-8.

14. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A Review of Combination Antimicrobial Therapy for Enterococcus faecalis Bloodstream Infections and Infective Endocarditis. Clin Infect Dis. 2018;67:303-9.

15. Pericàs JM, Cervera C, Moreno A, et al. Outcome of Enterococcus faecalis infective endocarditis according to the length of antibiotic therapy: Preliminary data from a cohort of 78 patients. PLoS One. 2018;13:e0192387.

16. Bouza E, Kestler M, Beca T, et al. The NOVA score: a proposal to reduce the need for transesophageal echocardiography in patients with enterococcal bacteremia. Clin Infect Dis. 2015;60:528-35.

17. Dahl A, Lauridsen TK, Arpi M, et al. Risk Factors of Endocarditis in Patients With Enterococcus faecalis Bacteremia: External Validation of the NOVA Score. Clin Infect Dis. 2016;63:771-5.

18. Berge A, Krantz A, Östlund H, Nauclér P, Rasmussen M. The DENOVA score efficiently identifies patients with monomicrobial Enterococcus faecalis bacteremia where echocardiography is not necessary. Infection. 2018 Sep 3.

19. Pericàs JM, Corredoira J, Moreno A, et al. Relationship Between Enterococcus faecalis Infective Endocarditis and Colorectal Neoplasm: Preliminary Results From a Cohort of 154 Patients. Rev Esp Cardiol (Engl Ed). 2017;70:451-8.

20. Pericàs JM, Corredoira J, Miró JM.Colorectal Adenomas. N Engl J Med. 2016;375:387-8.

21. Benito N, Miró JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. Ann Intern Med. 2009;150:586-94.

22. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30:633-8.

23. Durante-Mangoni E, Bradley S, Selton-Suty C, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med. 2008;168:2095-103.

24. Anderson DJ, Olaison L, McDonald JR, et al. Enterococcal prosthetic valve infective endocarditis: report of 45 episodes from the International Collaboration on Endocarditis-merged database. Eur J Clin Microbiol Infect Dis. 2005;24:665-70.

25. McDonald JR, Olaison L, Anderson DJ, et al. Enterococcal endocarditis: 107 cases from the international collaboration on endocarditis merged database. Am J Med. 2005;118:759-66.

26. Royer G, Melloul E, Roisin L, et al. Complete genome sequencing of Enterococcus faecalis strains suggests role of Ebp deletion in infective endocarditis relapse. Clin Microbiol Infect. 2019 Jul 12. pii: S1198-743X(19)30395-7. doi: 10.1016/j.cmi.2019.07.006.

27. Habib G, Lancellotti P, Antunes MJ, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36:3075-128.

404 28. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis,
405 Antimicrobial Therapy, and Management of Complications: A Scientific Statement for
406 Healthcare Professionals From the American Heart Association. Circulation 2015; 132:1435-
407 86.
408

Figure Legends

Central Illustration.

Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis.

(a) Kaplan-Meier curve for mortality at one year

(b) Kaplan-Meier curve for relapses over time.

436 **Table 1. Comparison of characteristics and outcome of enterococcal endocarditis and**
437 **endocarditis caused by other microorganisms from the GAMES Cohort (2008-2016).**

	Enterococcal IE (N=516)	**Non-enterococcal IE (N=3,308)**	***P***
Median age, years (IQR)	72 (64-78)	68 (55-77)	<0.001
Male sex (%)	357 (69.2%)	2206 (66.7%)	0.254
Comorbidities			
Diabetes mellitus	168 (32.6%)	913 (27.6%)	0.025
Chronic lung disease	139 (26.9%)	560 (16.9%)	<0.001
Ischemic cardiomyopathy	152 (29.5%)	841 (25.4%)	0.060
Congestive heart failure	197 (38.2%)	1077 (32.6%)	0.014
Moderate/severe liver disease	24 (4.7%)	144 (4.4%)	0.764
- Child Pugh score, mean (SD)	11 (2.83)	8.4 (2.46)	0.160
- MELD score, mean (SD)	20.6 (8.1)	19.7 (8.8)	0.733
Moderate/severe chronic renal failure	94 (18.2%)	489 (14.8%)	0.058
Hemodialysis	24 (4.7%)	157 (4.7%)	0.924
Neoplasm	94 (18.2%)	508 (15.4%)	0.114
Transplantation	9 (1.7%)	64 (1.9%)	0.760
Immunosuppressant therapy	38 (7.4%)	192 (5.8%)	0.201
IV drug use	5 (1%)	78 (2.4%)	0.006
HIV	4 (0.8%)	61 (1.8%)	0.018
Previous IE	63 (12.2%)	215 (6.5%)	<0.001
Congenital cardiac abnormality	5 (1%)	218 (6.6%)	<0.001

Non-congenital valve disease	252 (48.8%)	1431 (43.3%)	0.018
Median age-adjusted Charlson score (IQR)	5 (4-7)	4 (3-6)	<0.001
Type of endocarditis			
Native	324 (62.7%)	2007 (60.7%)	0.355
Prosthetic*	185 (35.8%)	955 (28.9%)	0.002
PCM/DF[+]	8 (1.5%)	346 (10.5%)	<0.001
Valve involvement[+]			
Aortic	332 (64.3%)	1545 (46.7%)	<0.001
Mitral	226 (43.8%)	1416 (42.8%)	0.672
Tricuspid	15 (2.9%)	186 (5.6%)	0.001
Pulmonary	0	51 (1.5%)	<0.001
Diagnosis of endocarditis according to modified Duke criteria			0.029
Definite	431 (83.5%)	2626 (79.4%)	
Possible	85 (16.5%)	682 (20.6%)	
Median time of symptoms duration until admission in non-nosocomial cases, days (IQR)	6.5 (1.3-22.8)	6.5 (2-18)	0.549
Source			
Oral	8 (1.6%)	220 (6.7%)	<0.001
Respiratory	2 (0.4%)	40 (1.2%)	0.096
Genitourinary	92 (17.8%)	106 (3.2%)	<0.001
Gastrointestinal	82 (15.9%)	172 (5.2%)	<0.001
Vascular	62 (12%)	637 (19.3%)	<0.001
Cutaneous	10 (1.9%)	260 (7.9%)	<0.001

Other	19 (3.8%)	202 (6.3%)	0.031
Unknown	262 (50.8%)	1708 (51.6%)	0.734
Etiology			NA
Enterococci			
E. faecalis	468 (90.7%)	-	
E. faecium	36 (7%)	-	
Other enterococci[±]	12 (2.3%)	-	
S. *aureus*	-	870 (26.3%)	
MSSA	-	849 97.6%)	
MRSA	-	21 (2.4%)	
Viridans group streptococci	-	616 (18.6%)	
Coagulase-negative staphylococci	-	664 (20.1%)	
Bovis group streptococci	-	244 (7.4%)	
Other streptococci	-	193 (5.8%)	
Other	-	711 (21.5%)[×]	
Acquisition			
Community	282 (54.7%)	1953 (59%)	0.062
Health-care associated	219 (42.4%)	1229 (37.1%)	0.093
Nosocomial	168 (32.6%)	954 (28.8%)	0.092
Non-nosocomial health-care associated	51 (9.9%)	275 (8.3%)	0.262
Unknown	15 (2.9%)	116 (3.5%)	0.486
Clinical complications			
New onset or worsening heart failure	232 (45%)	1270 (38.4%)	0.005
NYHA I	12 (5.2%)	114 (9%)	0.054

NYHA II	35 (15.1%)	214 (16.9%)	0.506
NYHA III	95 (40.9%)	413 (32.5%)	0.013
NYHA IV	90 (38.8%)	529 (41.6%)	0.416
Persistent bacteremia	69 (13.4%)	378 (11.4%)	0.223
CNS emboli	86 (16.7%)	663 (20%)	0.058
Hemorrhagic	11 (12.8%)	110 (16.6%)	0.367
Extensive (>2cm)	0	109 (16.4%)	0.001
Multiple (>3)	6 (7%)	68 (10.3%)	0.337
Other major emboli	95 (18.4%)	687 (20.8%)	0.202
Pulmonary emboli	6 (1.2%)	183 (5.5%)	<0.001
Vertebral osteomyelitis	18 (3.5%)	97 (2.9%)	0.479
Non-vertebral osteomyelitis	6 (1.2%)	52 (1.6%)	0.536
Renal abscess	14 (2.7%)	87 (2.6%)	0.914
Splenic abscess	66 (12.8%)	310 (9.4%)	0.028
Heart conduction abnormality	39 (7.6%)	297 (9%)	0.262
Acute renal failure	191 (37%)	1177 (35.6%)	0.530
Septic shock	37 (7.2%)	432 (13.1%)	<0.001
Echocardiographic findings			
TEE performed	391 (75.8%)	2583 (78.1%)	0.253
Median ejection fraction (IQR)	60% (55-65)	60% (55-65)	0.536
Median vegetation size in mm (IQR)	8 (3-14)	8 (3-14)	0.088
Moderate-severe aortic regurgitation	193 (37.4%)	882 (26.7%)	<0.001
Moderate-severe mitral regurgitation	197 (38.2%)	1111 (33.6%)	0.048
Perivalvular abscess	62 (12%)	514 (15.5%)	0.024

Intracardiac fistula	4 (0.8%)	86 (2.6%)	<0.001
Pseudoaneurysm	18 (3.5%)	183 (5.5%)	0.023
Leaflet perforation/rupture	70 (13.6%)	436 (13.2%)	0.082
Treatment characteristics			
Antibiotics properly indicated	493 (95.5%)	3168 (95.8%)	0.817
Median length of antibiotic treatment, days (IQR)	42 (30-46)	36 (24-44)	<0.001
Cardiac surgery			
Indicated	316 (61.2%)	2182 (66%)	0.040
Operated during admission	210 (40.7%)	1520 (45.9%)	0.024
New surgery during the first year after admission	23 (4.5%)	144 (4.4%)	0.915
Outcomes			
In-hospital mortality	123 (23.8%)	892 (27%)	0.123
Mortality at 1-year	159 (30.8%)	1100 (33.3%)	0.266
Relapses	18 (3.5%)	57 (1.7%)	0.035

HIV: Human immunodeficiency syndrome; IQR: Interquartile range; MSSA: methicillin-susceptible *S. aureus;* MRSA: methicillin-resistant *S. aureus*; NA: not analyzed; PCM/DF: pacemakers/defibrillators

[*] There were 17 cases of endocarditis over TAVI, 3 of them occurring in the EE group and 14 in the NEE group (0.5% vs. 0.4%, P=0.802).

[+]Only episodes in which only PCM/DF are affected are included in this group. Episodes have been classified as native or prosthetic valve where a concomitant valve involvement exists.

The sum does not equal 100% because episodes with multivalve involvement are also counted.

[±] In 9 cases there was not identification at the species level (*Enterococcus spp*.), whereas the 3 remaining cases corresponded to one case of *E. durans, E. avium* and *E. gallinarum* each.

[×]Negative culture: 342 (48.1%); Gram negative bacilli: 163 (22.9%); Polymicrobial: 69 (9.7%); *Candida spp*: 64 (9.0%); Anaerobic bacteria: 39 (5.5%); Other fungi: 11 (1.5%); Miscellany: 23 (3.2%).

453 **Table 2. Comparison of Health-Care acquired vs. Community-acquired Enterococcal**
454 **Endocarditis.**

	Community-acquired (N=282)	**Nosocomial-HCA (N=168)**	**Non-nosocomial HCA (N=51)**	***P***
Enterococcal species				0.342
E. faecalis	256 (90.8%)	153 (91.1%)	47 (92.2%)	
E. faecium	17 (6%)	15 (8.9%)	4 (7.8%)	
Other	9 (3.2%)*	0	0	
Median age, years (IQR)	73 (64-80)	73 (64-78)	71 (62-79)	0.332
Male sex (%)	195 (69.1%)	120 (71.4%)	31 (60.7%)	0.222
Comorbidities				
Diabetes mellitus	97 (34.4%)	46 (27.3%)	17 (33.3%)	0.296
Chronic lung disease	73 (25.9%)	49 (29.1%)	12 (23,5)	0.700
Ischemic cardiomyopathy	78 (27.7%)	56 (33.3%)	12 (23.5%)	0.285
Congestive heart failure	101 (35.8%)	74 (44%)	19 (37.2%)	0.221
Moderate/severe liver disease	8 (2.8%)	7 (4.2%)	8 (15.7%)	0.022
Moderate/severe chronic renal failure	43 (15.2%)	37 (22%)	12 (23.5%)	0.120
Hemodialysis	4 (1.4%)	11 (6.5%)	8 (15.6%)	<0.001
Neoplasm	49 (17.4%)	28 (16.6%)	13 (25.4%)	0.329
Transplantation	2 (0.7%)	6 (3.6%)	1 (2%)	0.806
Immunosuppressant therapy	15 (5.3%)	18 (10.7%)	4 (7.8%)	0.105
IV drug use	5 (1.8%)	0	0	0.024
HIV	4 (1.4%)	0	0	0.045

Previous IE	28 (9.9%)	24 (14.2%)	10 (19.6%)	0.101
Congenital cardiac abnormality	4 (1.4%)	2 (1.2%)	1 (2%)	0.918
Non-congenital valve disease	134 (47.5%)	89 (52.9%)	23 (45%)	0.445
Median age-adjusted Charlson score (IQR)	5 (4-7)	5 (4-7)	6 (4-8)	0.425
Type of endocarditis				
Native	192 (68.1%)	87 (51.7%)	37 (72.5%)	<0.001
Prosthetic	86 (30.5%)	79 (47%)	13 (25.4%)	<0.001
PCM/DF*	4 (1.4%)	3 (1.7%)	0	0.103
Valve involvement[+]				
Aortic	179 (63.5%)	105 (62.5%)	37 (72.5%)	0.403
Mitral	122 (43.3%)	75 (44.6%)	24 (47%)	0.868
Tricuspid	10 (3.5%)	4 (2.4%)	1 (2%)	0.398
Pulmonary	0	0	0	1.000
Clinical complications				
New onset or worsening heart failure	126 (44.7%)	78 (46.7%)	23 (45.1%)	0.849
Persistent bacteremia	36 (12.8%)	23 (13.7%)	8 (15.6%)	0.652
CNS emboli	43 (15.2%)	30 (17.8%)	10 (19.6%)	0.372
Other major emboli	57 (20.2%)	28 (16.7%)	6 (11.8%)	0.220
Pulmonary emboli	2 (0.7%)	4 (2.3%)	0	0.280
Vertebral osteomyelitis	9 (3.2%)	7 (4.1%)	2 (3.9%)	0.779
Non-vertebral osteomyelitis	5 (1.8%)	0	1 (1.9%)	0.152
Renal abscess	8 (2.8%)	0	0	0.695
Splenic abscess	40 (14.2%)	6 (3.5%)	3 (5.8%)	<0.001
Heart conduction abnormality	22 (7.8%)	12 (7.1%)	3 (5.8%)	0.880

Acute renal failure	112 (39.7%)	51 (30.3%)	19 (37.2%)	0.134
Septic shock	19 (6.7%)	14 (8.3%)	3 (5.8%)	0.761
Echocardiographic findings				
TEE performed	206 (73%)	134 (79.8%)	40 (78.4%)	0.093
Median ejection fraction (%, IQR)	60 (55-65)	60 (50-65)	60 (50-68)	0.465
Median vegetation size (mm, IQR)	8 (3-15)	10 (7-19)	10.5 (8-13)	0.729
Moderate-severe aortic regurgitation	107 (37.9%)	54 (32.1%)	24 (47%)	0.133
Moderate-severe mitral regurgitation	119 (42.2%)	49 (29.1%)	25 (49%)	0.006
Perivalvular abscess	23 (8.2%)	28 (16.6%)	9 (17.6%)	0.011
Intracardiac fistula	2 (0.7%)	2 (1.2%)	0	0.235
Pseudoaneurysm	5 (1.8%)	6 (3.6%)	5 (9.8%)	0.010
Leaflet perforation/rupture	44 (15.6%)	19 (11.3%)	6 (11.7%)	0.163
Treatment characteristics				
Median length of antibiotic treatment, days (IQR)	42 (29-46)	42 (33-47)	42 (28-46)	0.317
Cardiac surgery	121 (42.9%)	57 (33.9%)	23 (45.1%)	0.127
Outcomes				
In-hospital mortality	60 (21.3%)	45 (25.5%)	16 (31.3%)	0.186
One-year mortality	79 (28%)	53 (31.5%)	22 (43.1%)	0.094
Relapses[±]	10 (3.5%)	3 (1.7%)	4 (7.8%)	0.109

455 [*] 8 cases due to *Enterococcus spp*. and 1 case of *E. durans* IE

456 [±] One case of relapse among EE was not included because it had an unknown source of
457 acquisition.

458

459 **Table 3. Comparison of *E. faecalis* vs. non-*E. faecalis* Enterococcal Endocarditis**

	***E. faecalis* IE (N=468)**	***Non-E. faecalis* IE (N=48)**	***P***
Median age, years (IQR)	73 (64.5-79)	68.5 (59.5-76)	0.080
Male sex (%)	325 (69.4%)	32 (66.7%)	0.697
Comorbidities			
Diabetes mellitus	151 (32.3%)	17 (35.4%)	0.663
Chronic lung disease	130 (27.8%)	9 (18.8%)	0.133
Ischemic cardiomyopathy	140 (29.9%)	12 (25%)	0.457
Congestive heart failure	187 (40%)	10 (20.8%)	0.002
Moderate/severe liver disease	20 (4.3%)	4 (8.3%)	0.322
Moderate/severe chronic renal failure	88 (18.8%)	6 (12.5%)	0.217
Hemodialysis	24 (5.1%)	0	<0.001
Neoplasm	81 (17.3%)	13 (27.1%)	0.142
Transplantation	8 (1.7%)	1 (2.1%)	0.862
Immunosuppressant therapy	33 (7.1%)	5 (10.4%)	0.461
IV drug use	4 (0.9%)	1 (2.1%)	0.560
HIV	3 (0.6%)	1 (2.1%)	0.491
Previous IE	57 (12.2%)	6 (12.5%)	0.949
Congenital cardiac abnormality	6 (1.3%)	1 (2.1%)	0.706
Non-congenital valve disease	229 (48.9%)	23 (47.9%)	0.893
Median age-adjusted Charlson score (IQR)	5 (4-7)	5 (3-7)	0.227
Type of endocarditis			
Native	287 (61.3%)	37 (77.1%)	0.015
Prosthetic	174 (37.2%)	11 (22.9%)	0.028
PCM/DF*	7 (1.5%)	0	0.109

Valve involvement[+]			
Aortic	302 (64.5%)	30 (62.5%)	0.782
Mitral	203 (43.4%)	23 (47.9%)	0.549
Tricuspid	14 (3%)	1 (2.1%)	0.681
Pulmonary	0	0	1.000
Acquisition			
Community	256 (54.7%)	26 (54.2%)	0.944
Health-care associated	197 (42.1%)	22 (45.8%)	0.617
Nosocomial	153 (32.7%)	15 (31.3%)	0.838
Non-nosocomial health-care associated	44 (9.4%)	7 (14.6%)	0.326
Unknown	15 (3.2%)	0	0.124
Clinical complications			
New onset or worsening heart failure	214 (45.7%)	18 (37.5%)	0.264
Persistent bacteremia	61 (13%)	8 (16.7)	0.517
CNS emboli	75 (16%)	11 (22.9%)	0.274
Other major emboli	85 (18.2%)	10 (20.8%)	0.663
Pulmonary emboli	4 (0.9%)	2 (4.2%)	0.256
Vertebral osteomyelitis	17 (3.6%)	1 (2.1%)	0.577
Non-vertebral osteomyelitis	6 (1.3%)	0	0.358
Renal abscess	12 (2.6%)	2 (4.2%)	0.590
Splenic abscess	60 (12.8%)	6 (12.5%)	0.949
Heart conduction abnormality	36 (7.7%)	3 (6.3%)	0.697
Acute renal failure	172 (36.8%)	19 (39.6%)	0.702
Septic shock	31 (6.6%)	6 (12.5%)	0.232
Echocardiographic findings			
TEE performed	358 (76.5%)	33 (68.8%)	0.267
Median ejection fraction (IQR)	60 (55-66)	60 (55-65)	0.805

Median vegetation size, mm (IQR)	8 (3-14)	6 (3-8)	0.110
Moderate-severe aortic regurgitation	179 (38.2%)	14 (29.2%)	0.191
Moderate-severe mitral regurgitation	183 (39.1%)	14 (209.2%)	0.153
Paravalvular abscess	60 (12.8%)	2 (4.2%)	0.008
Intracardiac fistula	3 (0.6%)	1 (2.1%)	0.491
Pseudoaneurysm	16 (3.4%)	2 (4.2%)	0.803
Leaflet perforation/rupture	63 (13.5%)	7 (14.6%)	0.585
Treatment characteristics			
Median length of antibiotic treatment, days (IQR)	42 (30-46)	42 (28-44)	0.389
Cardiac surgery	192 (41%)	18 (37.5%)	0.632
Initial antibiotic treatment			
Double beta-lactam combination	318 (67.9%)	11 (22.9%)	<0.001
Beta-lactam plus aminoglycoside	96 (20.3%)	5 (10.4%)	0.092
Other	54 (11.4%)[±]	32 (66.7%)	<0.001
Outcomes			
In-hospital mortality	109 (23.3%)	14 (29.2%)	0.391
Mortality at 1-year	144 (30.8%)	15 (31.3%)	0.945
Relapses	16 (3.4%)	2 (4.2%)	0.803

± Vancomycin plus aminoglycoside: 11 (20.4%); Vancomycin plus other: 8 (14.8%); Daptomycin: 7 (13%); Daptomycin plus beta-lactam: 5 (9.3%); Daptomycin plus fosfomycin: 1 (1.8%); Beta-lactam alone: 7 (13%); Beta-lactam plus quinolone: 4 (7.4%); Linezolid: 2 (3.7%); Other: 9 (16.7%).

Table 4. Analysis of Risk Factors for In-Hospital Mortality, One-year Mortality and Relapses for 516 cases of Enterococcal Endocarditis.

	One-Year Mortality				Relapses			
	Univariate		***Multivariate***		***Univariate***		***Multivariate***	
	HR (95%CI)	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
E. faecalis	0.99 (0.58, 1.68)	0.970			0.71 (0.16, 3.14)	0.663		
Initial antibiotic treatment included gentamicin	N.A.				N.A.			
Male sex	0.94 (0.67, 1.31)	0.722			0.44 (0.16, 1.17)	0.103	0.50 (0.19, 1.36)	0.174
Age (years)	1.00 (0.99, 1.01)	0.534			1.02 (0.98, 1.07)	0.322		
Diabetes mellitus	1.56 (1.14, 2.14)	0.006	1.00 (0.63, 1.62)	0.972	0.69 (0.22, 2.14)	0.524		
Congestive heart failure	1.10 (0.80, 1.51)	0.561			0.98 (0.36, 2.70)	0.976		
Moderate-severe chronic renal failure	1.97 (1.40, 2.79)	<0.001			1.05 (0.30, 3.67)	0.943		
Moderate-severe liver disease	2.58 (2.52, 4.40)	<0.001	2.62 (1.31, 5.24)	0.007	2.95 (0.67, 12.96)	0.152	2.03 (0.45, 9.16)	0.351

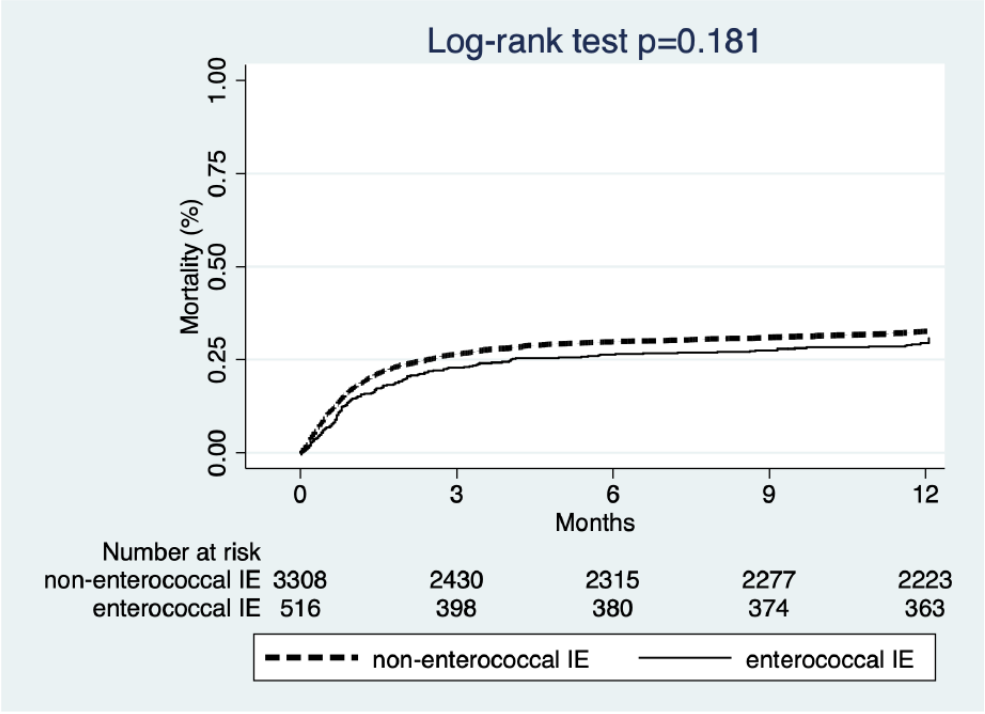
Previous IE	0.53 (0.30, 0.96)	0.041	0.42 (0.21, 0.84)	0.012	2.45 (0.79, 7.59)	0.124		
Age-adjusted Charlson score	1.16 (1.10, 1.23)	<0.001	1.12 (1.01, 1.24)	0.010	0.93 (0.76, 1.14)	0.497		
Community acquisition	0.79 (0.58, 1.08)	0.154			1.17 (0.42, 3.29)	0.765		
Prosthetic IE	0.78 (0.56, 1.09)	0.158			1.82 (0.68, 4.85)	0.232		
Urinary source	1.31 (0.89, 1.91)	0.172			0.65 (0.15, 2.85)	0.576		
Aortic valve IE	1.08 (0.78, 1.50)	0.623			0.42 (0.16, 1.14)	0.094	0.42 (0.16, 1.15)	0.095
Mitral valve IE	1.07 (0.79, 1.48)	0.602			2.15 (0.78, 5.92)	0.133	1.67 (0.49, 5.78)	0.412
Paravalvular complications*	1.52 (1.09, 2.12)	0.014	1.87 (1.22, 2.87)	0.040	0.19 (0.03, 1.43)	0.115	0.22 (0.03, 1.73)	0.153
Vegetation size ≥ 10mm	0.79 (0.46, 1.37)	0.414			0.96 (0.16, 5.72)	0.961		
New onset heart failure	2.37 (1.72, 3.27)	<0.001	2.42 (1.53, 3.83)	<0.001	0.94 (0.35, 2.52)	0.904		

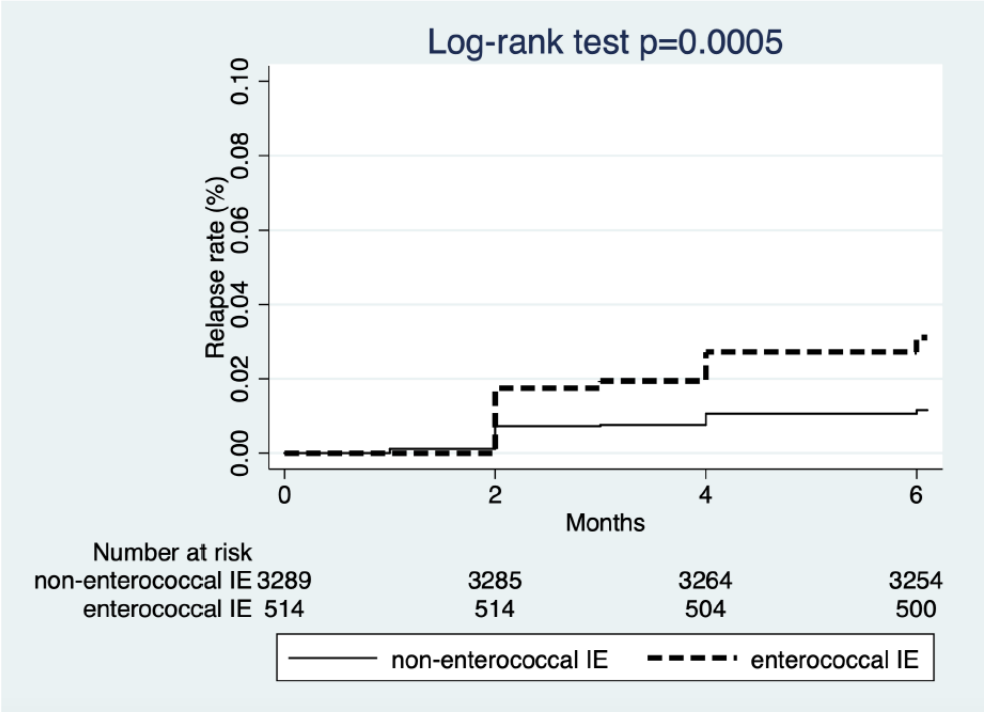
Persistent bacteremia	1.37 (0.90, 2.07)	0.143			3.99 (1.45, 10.98)	0.007	4.03 (1.43, 11.33)	0.008
CNS emboli	1.23 (0.83, 1.83)	0.313			1.12 (0.32, 3.94)	0.852		
Other emboli	1.05 (0.71, 1.57)	0.787			0.99 (0.28, 3.48)	0.993		
New heart conduction abnormality	1.58 (0.94, 2.66)	0.082			N.A.			
Acute renal failure	1.86 (1.36, 2.54)	<0.001	1.30 (0.84, 2.00)	0.241	1.31 (0.49, 3.52)	0.589		
Septic shock	3.09 (1.99, 4.77	<0.001	1.76 (1.04, 2.99)	0.033	N.A.			
Inappropriate initial antibiotics	1.71 (0.90, 3.25)	0.102			N.A.			
Cardiac surgery	0.62 (0.45, 0.87)	0.006	0.88 (0.54, 1.43)	0.613	0.33 (0.09, 1.15)	0.083	0.48 (0.13, 1.71)	0.253
Logistic EuroSCORE	1.02 (1.01, 1.03	<0.001	1.02 (1.01, 1.03)	0.002	1.00 (0.98, 1.03)	0.923		

467 * Paravalvular complications include at least one of the following: periannular abscess, pseudoaneurysm, fistula, or leaflet perforation/rupture.

468 N.A.= Non-assessed due to low number of events

Central Illustration. Mortality and relapses in enterococcal endocarditis vs. non-enterococcal endocarditis. (a) Kaplan-Meier curve for mortality at one year; (b) Kaplan-Meier curve for relapses over time.



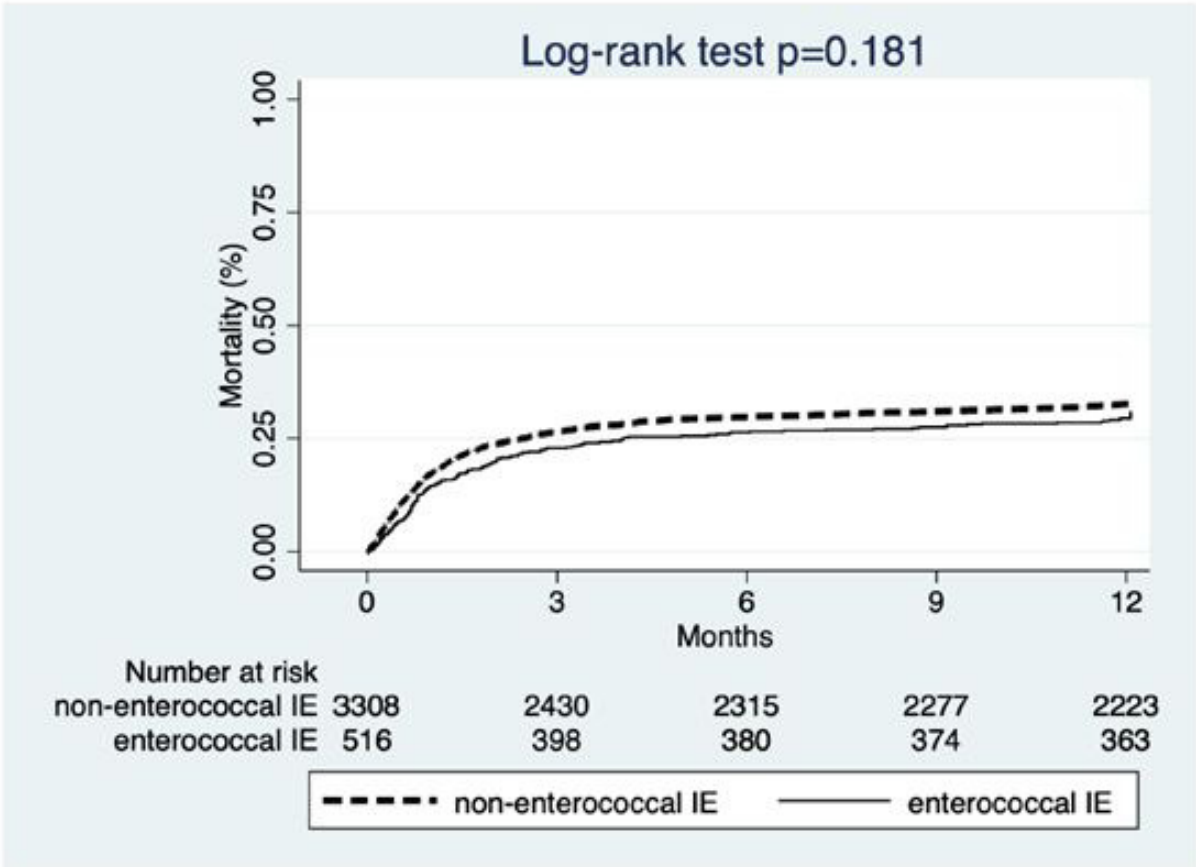


Clinical areas and patient features in which enterococcal endocarditis is of special relevance:

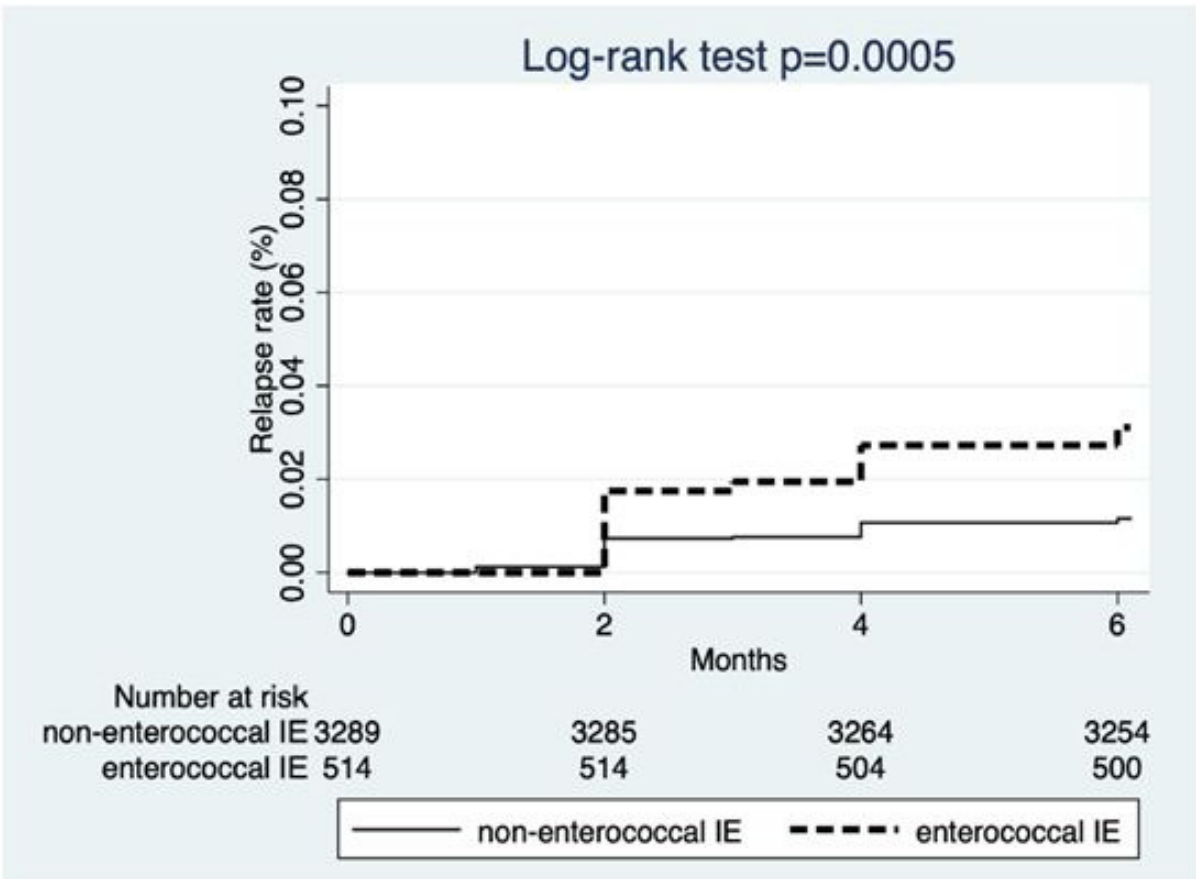
- Elderly patients
- TAVI*
- Prosthetic valve endocarditis
- Degenerative left-sided valve disease
- Aortic involvement
- Chronic lung disease
- Chronic heart failure
- Hemodialysis*****

* Shown in other large series

a.


Log-rank test p=0.181
Mortality (%)
0.00
0.25
0.50
0.75
1.00
0
3
6
9
12
Months
Number at risk
non-enterococcal IE 3308 2430 2315 2277 2223
enterococcal IE 516 398 380 374 363
non-enterococcal IE
enterococcal IE

b.


Log-rank test p=0.0005
Relapse rate (%)
0.00
0.02
0.04
0.06
0.08
0.10
0
2
4
6
Months
Number at risk
non-enterococcal IE 3289 3285 3264 3254
enterococcal IE 514 514 504 500
non-enterococcal IE
enterococcal IE